



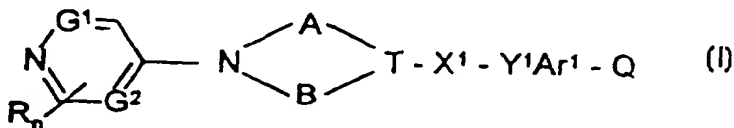
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<p>(21) International Application Number: PCT/GB97/00282 (22) International Filing Date: 31 January 1997 (31.01.97) (30) Priority Data: 9602157.1 2 February 1996 (02.02.96) GB 9602156.3 2 February 1996 (02.02.96) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BROWN, George, Robert [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). STOKES, Elaine, Sophie, Elizabeth [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WATERSON, David [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WOOD, Robin [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). WATKINS, William, John [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). NEWCOMBE, Nicholas, John [GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). CUMMING, John, Graham</p>		<p>[GB/GB]; Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (74) Agent: BILL, Kevin; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>

(54) Title: HETEROCYCLIC COMPOUNDS USEFUL AS PHARMACEUTICAL AGENTS

(57) Abstract

Compounds of formula (I) in which all variables are defined in the description and their salts inhibit the enzyme oxido squalene cyclase and are useful in treating hypercholesterolemia and also as anti-fungal agents. Processes for their preparation are also described together with their use in medicine.



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HETEROCYCLIC COMPOUNDS USEFUL AS PHARMACEUTICAL AGENTS.

This invention concerns heterocyclic compounds which are useful in inhibiting
5 oxido-squalene cyclase, processes for their preparation and pharmaceutical compositions
containing them. The present invention is also concerned with heterocyclic compounds
capable of inhibiting cholesterol biosynthesis and hence in lowering cholesterol levels in
blood plasma. The present invention also relates to methods of using such heterocyclic
compounds in diseases and medical conditions such as hypercholesterolemia and
10 atherosclerosis.

There is clinical evidence that raised serum cholesterol levels increase the risk of
coronary heart disease and associated diseases such as atherosclerosis and ischaemic heart
disease. As a result there has been a great deal of interest in finding ways of lowering
cholesterol levels in blood plasma. Although it has been possible to obtain some reduction by
15 means of diet, only modest reductions have been obtained by controlling the dietary intake of
cholesterol. Consequently, there is a need for therapeutic approaches to reducing cholesterol
levels.

Several different classes of compounds have been reported to possess the
capability of being able to lower cholesterol levels in blood plasma. For example agents
20 which inhibit the enzyme HMGCoA reductase, which is essential for the production of
cholesterol, have been reported to reduce levels of serum cholesterol. Illustrative of this class
of compounds is the HMGCoA reductase inhibitor known as lovastatin which is disclosed in
US Patent No 4,231,938. Other agents which are reported to lower serum cholesterol include
those which act by complexing with bile acids in the intestinal system and which are hence
25 termed "bile acid sequestrants". It is believed that many of such agents act by sequestering
bile acids within the intestinal tract. This results in a lowering of the levels of bile acid
circulating in the enterohepatic system and promotes replacement of bile acids by synthesis
in the liver from cholesterol, which results in an upregulation of the hepatic LDL cholesterol
receptor and in a lowering of circulating blood cholesterol levels.

30 The biosynthesis of cholesterol is a complex process which will be considered
here as three principal stages, namely 1) the conversion of acetic acid to mevalonic acid 2) the
conversion of mevalonic acid to squalene and 3) the conversion of squalene to cholesterol. In

the last stage, squalene is first converted into 2,3-oxido-squalene and then to lanosterol.

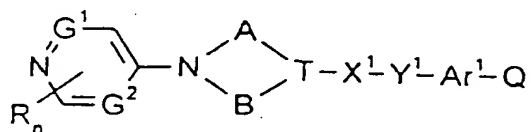
Lanosterol is then converted to cholesterol through a number of enzymatic steps.

The conversion of 2,3-oxido-squalene to lanosterol is a key step in the biosynthesis of cholesterol. This conversion is catalysed by the enzyme oxido-squalene cyclase. It follows that inhibition of this enzyme decreases the amount of lanosterol available for conversion to cholesterol. Consequently, inhibition of oxido-squalene cyclase should interrupt cholesterol biosynthesis and give rise to a lowering of cholesterol levels in blood plasma via LDL receptor upregulation.

The present invention is based on the discovery that certain heterocyclic compounds are inhibitors of oxido-squalene cyclase and are hence useful in treating diseases and medical conditions in which inhibition of oxido-squalene cyclase is desirable.

According to the present invention there is provided a compound of formula I: or a pharmaceutically acceptable salt thereof, wherein

According to the present invention there is provided a compound of formula I,



wherein

G¹ is CH or N;

G² is CH or N;

n is 1 or 2;

R is hydrogen, halogeno, trifluoromethyl, trifluoromethoxy, cyano, amino, hydroxy, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di(1-4C)alkylamino or phenyl(1-4C)alkyl;

A is methylene or ethylene; B is ethylene; and wherein A and B may independently optionally bear a substituent selected from (1-6C)alkyl, (1-6C)alkoxy, phenyl(1-4C)alkyl, halogeno and (1-6C)alkoxycarbonyl;

T is CH or N;

when T is CH, X¹ is selected from CR¹R², SO₂, SO, CO, CR³R⁴O, a bond, O, S and NR⁵; and when T is N, X¹ is selected from CR¹R², SO₂, SO, CO, CR³R⁴O and a bond;

wherein R¹, R², R³, R⁴ and R⁵ are independently selected from hydrogen and (1-4C)alkyl;

Y¹ represents CR⁶R⁷ or a bond, wherein R⁶ and R⁷ are independently selected from hydrogen and (1-4C)alkyl;

Ar¹ is a phenylene, naphthylene, a 5- or 6-membered monocyclic heteroaryl ring containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur, or a 9- or 10- membered bicyclic heteroaryl ring containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur;

Q is selected from hydrogen and a group of formula L¹X²L²Z in which L¹ is a bond, (1-4C)alkylene or (2-4C)alkenylene, L² is a bond or (1-4C)alkylene, X² is a bond, O, S, SO, SO₂, CR⁸R⁹, CO, OSO₂, OCR⁸R⁹, OCO, SO₂O, CR⁸(R⁹)O, COO, NR¹⁰SO₂, SO₂NR¹⁰,
10 NR¹¹CO, CONR¹¹, NR¹²CONR¹³ and NR¹⁴ in which R⁸ and R⁹ are independently selected from hydrogen, hydroxy and (1-4C)alkyl; and R¹⁰, R¹¹, R¹², R¹³ and R¹⁴ are independently selected from hydrogen and (1-4C)alkyl;

Z is hydrogen, (1-4C)alkyl, phenyl, naphthyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl or a heterocyclic moiety containing 1, 2, 3 or 4 heteroatoms selected from
15 nitrogen, oxygen and sulphur;

and wherein the phenyl, naphthyl or heteroaryl moiety in Ar¹ and the alkyl, phenyl, naphthyl, or heterocyclic moiety in Z may optionally bear one or more substituents selected from halogeno, hydroxy, oxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (1-4C)alkylenedioxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, di-N[(1-6C)alkyl]carbamoyl, (1-6C)alkanoylamino, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno(1-6C)alkyl, halogeno(1-6C)alkylthio, halogeno(1-6C)alkoxy, (1-6C)alkanoyl, tetrazoyl, phenyl, phenoxy, phenylsulphonyl, piperidinocarbonyl, morpholinocarbonyl, hydroxy(1-6C)alkyl and
25 amino(1-6C)alkyl; wherein any phenyl containing substituents may optionally bear one or more substituents selected from halogeno, trifluoromethyl, trifluoromethoxy, cyano, amino, hydroxy, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di(1-4C)alkylamino;

provided that the compound is not N-[4-[4-(4-pyridyl)piperazin-1-ylcarbonyl]phenyl]-(E)-4-chlorostyrenesulphonamide or N-[4-[4-(4-pyridyl)piperazin-1-ylcarbonyl]phenyl]-4'-
30 bromo-4-biphenylesulphonamide;

and pharmaceutically acceptable salts thereof.

The chemical formulae referred to herein by Roman numerals are, for convenience, set out on a separate sheet following the Examples.

It will be understood that when formula I compounds contain a chiral centre, the compounds of the invention may exist in, and be isolated in, optically active or racemic form. The invention includes any optically active or racemic form of a compound of formula I which possesses the beneficial pharmacological effect of inhibiting oxido-squalene cyclase. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by, resolution of a racemic form, by synthesis from optically active starting materials or by asymmetric synthesis. It will also be appreciated that certain compounds of formula I may exist as geometrical isomers. The invention includes any geometrical isomer of a compound of formula I which possesses the beneficial pharmacological effect of inhibiting oxido-squalene cyclase.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of inhibiting oxido-squalene cyclase.

It is also to be understood that generic terms such as "alkyl" include both the straight chain and branched chain groups such as butyl and tert-butyl. However, when a specific term such as "butyl" is used, it is specific for the straight chain or "normal" butyl group, branched chain isomers such as "t-butyl" being referred to specifically when intended.

In one embodiment of the present invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, as herein before defined, provided that when X^1 is CO, Ar^1 is phenylene which optionally bears 1 or 2 substituents selected from halogeno, trifluoromethyl, (1-4C)alkyl and (1-4C)alkoxy, and L^2 is a bond to Q, then X^2 is a bond.

Particular values for optional substituents which may be present on a phenyl, naphthyl, heteroaryl or heterocyclic moiety include, for example,

- | | |
|----------------------|---|
| for alkyl; | (1-4C)alkyl, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl; |
| 30 for cycloalkyl | cyclopropyl, cyclobutyl or cyclopentyl; |
| for cycloalkyl alkyl | (3-6C)cycloalkyl(1-2C)alkyl such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl or cyclopentylmethyl; |

	for alkenyl;	(2-4C)alkenyl, such as allyl, prop-1-enyl, 2-methyl-2-propenyl or 2-butenyl;
	for alkynyl;	(2-4C)alkynyl, such as prop-2-ynyl or but-2-ynyl;
	for alkoxy;	(1-6C)alkoxy, such as methoxy, ethoxy, propoxy,
5		isopropoxy, butoxy, pentoxy or 3-methylbutoxy;
	for alkylamino;	(1-4C)alkylamino, such as methylamino, ethylamino, propylamino or butylamino;
	for di-alkylamino;	di-[(1-4C)alkyl]amino such as dimethylamino, diethylamino, methylpropylamino or dipropylamino;
10	for alkylcarbamoyl;	(1-4C)alkylcarbamoyl such as N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-butylcarbamoyl or N-tert-butylcarbamoyl or (N-(2-methylpropyl)carbamoyl;
	for di-alkylcarbamoyl;	di-[(1-4C)alkyl]carbamoyl, such as N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl;
15	for alkoxycarbonyl;	(1-4C)alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl, butoxycarbonyl or tert-butoxycarbonyl;
	for alkylthio;	(1-4C)alkylthio such as methylthio, ethylthio, propylthio, isopropylthio or butylthio;
20	for alkylsulphinyl;	(1-4C)alkylsulphinyl such as methylsulphinyl, ethylsulphinyl, propylsulphinyl, isopropylsulphinyl or butylsulphinyl;
	for alkylsulphonyl;	(1-4C)alkylsulphonyl such as methylsulphonyl, ethylsulphonyl, propylsulphonyl, isopropylsulphonyl or butylsulphonyl;
25	for halogeno;	fluoro, chloro, bromo or iodo;
	for halogenoalkyl;	halogeno(1-4C)alkyl such as halogenoalkyl containing one, two or three halo groups selected from fluoro, chloro, bromo and iodo and an alkyl group selected from methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl and sec-butyl, thus particular values will include
30		trifluoromethyl, difluoromethyl and fluoromethyl;
	for alkanoylamino;	(1-4C)alkanoylamino such as formamido, acetamido, propionamido, iso-propionamido, butyramido or iso-butyramido;

- for alkylenedioxy: methylenedioxy or ethylenedioxy;
- for alkanoyl: (1-4C)alkanoyl such as formyl, acetyl, propionyl or butyryl;
- for hydroxyalkyl 1-hydroxy-1-methylethyl, hydroxymethyl, 2-hydroxyethyl, or 2-hydroxypropyl;
- 5 for aminoalkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl or aminopropyl.

Particular values for optional substituents on A and B include, for example:

- for alkyl: (1-4C)alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl;
- 10 for alkoxy: (1-4C)alkoxy such as methoxy, ethoxy, propoxy, isopropoxy or butoxy;
- for phenylalkyl: phenyl (1-2C)alkyl such as benzyl, 2-phenylethyl or 1-phenylethyl
- for halogeno: fluoro, chloro, bromo or iodo
- 15 for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl or butoxycarbonyl;

Particular values for R include, for example.

- 20 for alkyl: methyl, ethyl, propyl, iso-propyl or tert-butyl;
- for alkoxy methoxy, ethoxy, propoxy, isopropoxy or butoxy;
- for alkylamino methylamino, ethylamino or propylamino;
- for di-alkylamino dimethylamino, *N*-ethyl-*N*-methylamino or diethylamino;
- for halogeno fluoro, chloro, bromo or iodo.

25

A particular value for R when trifluoromethyl is 3-trifluoromethyl and/or 5-trifluoromethyl. A further particular value for R is hydrogen, also (1-2C) alkyl, for example 2-methyl.

A particular value for Ar¹ when it is a 5- or 6-membered heteroaryl ring is, for
 30 example, furandiyl, thiophenediyl, pyridinediyl, pyrazinediyl, pyrimidinediyl, pyridazinediyl, pyrrolediyl, pyrazolediyl, imidazolediyl, oxazolediyl, isoxazolediyl, thiazolediyl, isothiazolediyl, 1,2,3-triazolediyl, 1,2,4-triazolediyl, oxadiazolediyl, furazandiyl.

thiadiazolediyl and 1,3,5-triazinediyl which may be attached through any available position including any available nitrogen atom. It will be appreciated that when $Q = H$ the ^Aabove group will only have one position of attachment and so group such as furandiyl will be furanyl etc.

- 5 A particular value for Z when it is a heterocyclic moiety is, for example, a monocyclic 5- or 6-membered heterocyclic ring or a 5- or 6-membered heterocyclic ring which is fused to a benzene moiety. Thus, particular values will include, furyl, benzofuranyl, thienyl, benzothienyl, pyridyl, quinolyl, isoquinolyl, 1,2,3,4-tetrahydroquinolyl, 1,2,3,4-tetrahydroisoquinolyl, pyrimidinyl, pyrazinyl, pyrrolyl, indolyl, indoliny, benzimidazolyl, 10 oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzthiazolyl and oxadiazolyl.

A particular value for R^1 to R^{14} when alkyl, is, for example methyl, ethyl, propyl, isopropyl and tert-butyl.

A particular value for L^1 or L^2 when alkylene is, for example, methylene, ethylene or trimethylene.

- 15 A particular value for Ar^1 when naphthyl is, for example, 1-naphthyl or 2-naphthyl.

A particular value for Ar^1 when phenylalkenyl is, for example, styryl, cinnamyl or 3-phenylprop-2-enyl.

A particular value for Ar^1 when phenylalkynyl is, for example, 2-phenylethynyl, 3-phenylprop-2-ynyl or 2-phenylprop-1-ynyl.

- 20 A particular value for A is methylene.

A particular value for T is CH.

More particularly, G^2 is CH or N; G^1 is CH.

More particular values are G^1 is CH or N; G^2 is CH.

More particularly when T is N, X^1 is selected from a bond, CO, SO_2 , and CR^1R^2 .

- 25 More particularly when T is CH, X^1 is selected from a bond, CO, SO_2 , CR^1R^2 and O.

More particularly Y^1 is a bond.

More particularly, Ar^1 is selected from a phenylene ring and a 6-membered heteroaryl moiety selected from these mentioned above.

- More particularly, Q is selected from hydrogen and a group of formula $L^1X^2L^2Z$ in 30 which L^1 is (1-4C)alkylene or a bond, X^2 is selected from NR^{12} CO, $NR^{16}SO_2$, $NR^{13}COR^{14}$ and SO_2 , and L^2 is a bond or (1-4C)alkylene; and Z is as defined above.

More particularly X^1-Y^1 taken together are O or S.

- In general, it is preferred that G^1 and G^2 are both CH.
- 4 In general, it is preferred that when Q is hydrogen, X^1 is selected from CR^1R^2 , SO_2 and CO.
- In general, it is preferred that L^1 and L^2 are selected from CH_2 and a bond.
- 5 In general, it is preferred that when Q is a group of formula $L^1X^2L^2Z$, X^1 is a bond.
- In general, it is preferred that T is N.
- In general, it is preferred that Ar^1 is a phenylene ring or a pyridyl ring.
- In general, it is preferred that Z is a phenyl, phenyl(2-4C)alkenyl, or naphthyl moiety.
- In general it is preferred that Ar^1 and Ar^2 , if substituted are independently mono- or di-
- 10 substituted.
- More preferably, Ar^1 is a phenylene ring optionally substituted as hereinbefore defined.
- More preferably, Z is a phenyl ring, optionally substituted as hereinbefore defined.
- More preferably A and B are both ethylene.
- 15 A specific value for G^1 is CH or N.
- A specific value for G^2 is CH or N (especially CH).
- A specific value for T is CH or N.
- A specific value for X^1 is a bond, CO, SO_2 , CH_2 and O. A further specific value is O or S.
- 20 A specific value for Ar^1 is a phenylene ring or a pyridyl ring. In particular the pyridyl ring is 2-pyridyl. More particular values include furanyl, pyrimidinyl, thiazolyl and oxazolyl.
- A specific value for the group $L^1X^2L^2$ is CH_2NHSO_2 , $NHSO_2$, CH_2SO_2 , $CH_2NHCONH$, CH_2NHCO , $CH_2N(Me)SO_2$, SO_2 , CO, O, CH_2 , OCH_2 , CH_2CH_2O , $COCH_2CH_2$ and a bond.
- 25 Further specific values for the group $L^1X^2L^2$ include CH_2NHCO , $NHSO_2$, CH_2NHSO_2 , CH_2NH , CONH and SO_2 .
- A specific value for Z is phenyl, styryl and naphthyl.
- A specific value for A is unsubstituted ethylene or unsubstituted methylene.
- A specific value for B is unsubstituted ethylene.
- 30 A suitable pharmaceutically-acceptable salt of an aminoheterocyclic derivative of the invention is, for example, an acid-addition salt of an aminoheterocyclic derivative of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an

inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of an aminoheterocyclic derivative of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

In one embodiment of the present invention there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein

10 G^1 is CH or N;

G^2 is CH or N;

n is 1 or 2;

R is hydrogen, halogeno, trifluoromethyl, trifluoromethoxy, cyano, amino, hydroxy, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino or di(1-4C)alkylamino;

15 A is methylene or ethylene; B is ethylene; and wherein A and B may independently optionally bear a substituent selected from (1-6C)alkyl, (1-6C)alkoxy, phenyl (1-4C)alkyl, halogeno and (1-6C)alkoxycarbonyl;

T is CH or N;

when T is CH, X^1 is selected from CR^1R^2 , SO_2 , SO, CO, a bond, CR^3R^4O , O, S and NR^5 , and when T is N, X^1 is selected from CR^1R^2 , SO_2 , SO, CO, CR^3R^4O and a bond, wherein R^1 , R^2 , R^3 , R^4 and R^5 are independently selected from hydrogen and (1-4C)alkyl;

Y^1 represents CR^6R^7 or a bond, wherein R^6 and R^7 are independently selected from hydrogen and (1-4C)alkyl;

Ar^1 is a phenylene ring or a 5- or 6-membered monocyclic heteroaryl ring containing 25 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur;

Q is selected from hydrogen and a group of formula $L^1X^2L^2Z$ in which L^1 is a bond or (1-4C)alkylene, L^2 is a bond or (1-4C)alkylene, X^2 is a bond, S, SO, SO_2 , CR^8R^9 , CO, $NR^{10}SO_2$, SO_2NR^{11} , $NR^{12}CO$, $CONR^{12}$ and $NR^{13}CONR^{14}$ in which R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are independently selected from hydrogen and (1-4C)alkyl;

30 Z is selected from phenyl, naphthyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl and a heterocyclic moiety containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur;

and wherein the phenyl or heteroaryl moiety in Ar¹ and the phenyl, naphthyl, or
heterocyclic moiety in Z may optionally bear one or more substituents selected from
halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-
6C)alkynyl, (1-6C)alkoxy, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (1-
4C)alkylenedioxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, di-
N[(1-6C)alkyl]carbamoyl, (1-6C)alkanoylamino, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-
6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, (1-
6C)alkanoyl and tetrazoyl;

provided that the compound is not N-[4-[4-(4-pyridyl)piperazin-1-yl]carbonyl]phenyl]-
(E)-4-chlorostyrenesulphonamide,

and pharmaceutically acceptable salts thereof.

Particular, prepared and specific values include the appropriate values mentioned
above. In a particular aspect of this embodiment when X¹ is CO, Ar¹ is phenylene which
optionally bears 1 or 2 substituents selected from halogeno, trifluoromethyl, (1-4C)alkyl and
(1-4C)alkoxy, and L² is a bond to Q, then X² is not a bond.

In a further embodiment of the present invention Q is hydrogen and G¹, G², R, n, A,
B, T, X¹, Ar¹ and the optional substituents for the phenyl or heteroaryl moieties in Ar¹ may
have any of the values hereinbefore defined.

Particular compounds of this embodiment include compounds of formula I and their
pharmaceutically acceptable salts in which R, n, Z, the optional substituents for a phenyl or
heteroaryl moiety on Ar¹ and the optional substituents for A and B may take the values
hereinbefore defined, (unless stated otherwise) and:-

(a) G¹ is CH or N; G² is CH; T is N or CH; when T is N, X¹ is CR¹R², SO₂, CO; when T
is CH, X¹ is CR¹R², SO₂, CO, O, S, NR³ or a bond, in which R¹, R² and R³ are independently
selected from hydrogen and (1-4C)alkyl; Y¹ is a bond, A and B are both ethylene; Ar¹ is a
phenyl ring;

(b) G¹ is CH or N; G² is CH, T is N, X¹ is CH₂, SO₂ or CO. A and B are ethylene, Y¹ is a
bond, Ar¹ is a phenyl ring;

(c) G¹ is CH, G² is CH, T is N, X¹ is CH₂, SO₂ or CO, A and B are ethylene, Y¹ is a bond,
Ar¹ is a phenyl ring;

(d) G¹ is CH or N, G² is CH, T is CH, A is methylene, B is ethylene, X¹ is O or a bond, Y¹
is a bond, Ar¹ is a phenyl or pyridyl ring;

(e) G^1 is CH or N, G^2 is CH, T is N, X^1 is CH_2 , SO_2 , CO. A and B are ethylene. Y^1 is a bond. Ar^1 is a pyridyl ring;

or additionally (f) which is as (d) above but wherein X^1 is O or S. It will be appreciated that Q is H in each of the above.

5 Further particular compounds of this embodiment ($Q = H$), include compounds of formula I and their pharmaceutically acceptable salts in which R, n, the optional substituents for a phenyl or heteroaryl moiety on Ar^1 and the optional substituents for A and B may take the values hereinbefore defined, (unless stated otherwise) and:-

(a) G^2 is CH or N; G^1 is CH; T is N or CH; when T is N, X^1 is CR^1R^2 , SO_2 , CO; when T is CH, X^1 is CR^1R^2 , SO_2 , CO, O, S, NR^3 or a bond, in which R^1 , R^2 and R^3 are independently selected from hydrogen and (1-4C)alkyl; Y^1 is a bond, A and B are both ethylene; Ar^1 is a phenyl ring;

(b) G^2 is CH or N; G^1 is CH, T is N, X^1 is CH_2 , SO_2 or CO, A and B are ethylene. Y^1 is a bond. Ar^1 is a phenyl ring;

15 (c) G^2 is CH or N, G^1 is CH, T is CH, A is methylene, B is ethylene. X^1 is O or a bond, Y^1 is a bond, Ar^1 is a phenyl or pyridyl ring;

(d) G^2 is CH or N, G^1 is CH, T is N, X^1 is CH_2 , SO_2 , CO, A and B are ethylene, Y^1 is a bond, Ar^1 is a pyridyl ring;

or additionally (e) which is as (c) above but wherein X^1 is O or S.

20 In a further embodiment of the present invention, Q is a group of formula $L^1X^2L^2Z$ and G^1 , G^2 , R, n, A, B, T, X^1 , Ar^1 , Z and the optional substituents for the phenyl, naphthyl, heteroaryl and heterocyclic moieties in Ar^1 and Z are as defined above.

Particular compounds of this embodiment include compounds of formula I and their pharmaceutically acceptable salts in which R, n, Ar^1 , Z the optional substituents for A and B and the optional substituents for a phenyl, heteroaryl, naphthyl or benzene moieties in Ar^1 or Z may take the values hereinbefore defined (unless stated otherwise) and:-

(a) G^1 is CH or N, G^2 is CH, T is N or CH, A is ethylene, or methylene, B is ethylene. X^1 and Y^1 are bonds, Q is a group of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene or a bond, X^2 is selected from $CONR^{12}$, $NR^{12}CO$, $NR^{10}SO_2$, $NR^{13}CONR^{14}$ and SO_2 , L is a (1-4C)alkylene or a bond, R^{10} .

30 R^{12} , R^{13} and R^{14} are independently selected from hydrogen and (1-4C)alkyl;

- (b) G^1 is CH or N, G^2 is CH, T is N or CH, A and B are ethylene. X^1 and Y^1 are bonds; Q is a group of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene or a bond, X^2 is NHCO, NHSO₂, NHCONH or SO₂, L^2 is (1-4C)alkylene or a bond, and R and n are as hereinbefore defined;
- (c) G^1 is CH, G^2 is CH, T is N or CH, A and B are ethylene. X^1 and Y^1 are bonds, Q is $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene, L^2 is a bond, X^2 is NHCO, NHSO₂, NHCONH and SO₂, or
- (d) G^1 is CH or N (preferably CH), G^2 is CH; T is N or CH (preferably N), X^1 and Y^1 are bonds, A and B are ethylene, Ar^1 is phenyl, Q is a group of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene or a bond (preferably alkylene such as CH₂), X^2 is NHCO, NHSO₂, NHCONH or SO₂, L^2 is (1-4C)alkylene or a bond (preferably a bond);

Further particular compounds of this embodiment include compounds of formula I and their pharmaceutically acceptable salts in which R, n, Ar^1 , Z the optional substituents for A and B and the optional substituents for a phenyl, heteroaryl, naphthyl or benzene moieties in Ar^1 or Z may take the values hereinbefore defined (unless stated otherwise) and:-

- 15 (a) G^2 is CH or N, G^1 is CH, T is N or CH, A is ethylene, or methylene, B is ethylene. X^1 and Y^1 are bonds, Q is a group of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene or a bond, X^2 is selected from CONR¹², NR¹²CO, NR¹⁰SO₂, NR¹³CONR¹⁴ and SO₂, L is a (1-4C)alkylene or a bond, R¹⁰, R¹², R¹³ and R¹⁴ are independently selected from hydrogen and (1-4C)alkyl;
- 20 (b) G^2 is CH or N, G^1 is CH, T is N or CH, A and B are ethylene. X^1 and Y^1 are bonds; Q is a group of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene or a bond, X^2 is NHCO, NHSO₂, NHCONH or SO₂, L^2 is (1-4C)alkylene or a bond, and R and n are as hereinbefore defined;
- (c) G^2 is CH or N (preferably CH), G^1 is CH; T is N or CH (preferably N), X^1 and Y^1 are bonds, A and B are ethylene, Ar^1 is phenyl, Q is a group of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene or a bond (preferably alkylene such as CH₂), X^2 is NHCO, NHSO₂, NHCONH or SO₂, L^2 is (1-4C)alkylene or a bond (preferably a bond);

In a preferred embodiment there is provided a compound of formula I or a pharmaceutically acceptable salt thereof, wherein:

- G^1 is CH, G^2 is CH, T is N, X^1 is CO, SO₂ or CH₂, A and B are ethylene, Ar^1 is phenyl, Q is hydrogen, and R, m and the optional substituent for the phenyl moiety of Ar^1 are as hereinbefore defined.

Particular, preferred and specific values include the appropriate values mentioned above.

In a further preferred embodiment there is provided a compound of formula I or a pharmaceutically acceptable salt thereof wherein:

5 G¹ is CH, G² is CH, T is N, X¹ is a bond, Y¹ is a bond, A and B are ethylene. Ar¹ is phenyl, Q is of formula L¹X²L²Z in which L¹ is (1-4C)alkylene (preferably CH₂), X² is NR⁶SO₂ in which R⁶ is (1-4C)alkyl or hydrogen (preferably hydrogen), and Z is phenyl, wherein the phenyl moiety of Ar¹ and Z may optionally be substituted as hereinbefore defined and R and m are as hereinbefore defined.

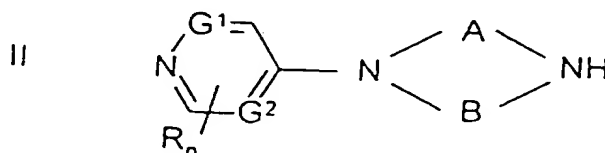
10 Particular, preferred and specific values include the appropriate values mentioned above.

In a further embodiment of the present invention, Z is (1-4C)alkyl or hydrogen; more particularly (1-4C)alkyl, and the other groups are as hereinbefore defined.

Compounds of particular interest include the compounds described in the
15 accompanying examples and as such they and their pharmaceutically acceptable salts are provided as a further feature of the present invention.

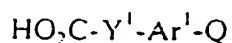
The compounds of formula I and their pharmaceutically acceptable salts may be prepared by processes known to be applicable to the preparation of structurally related compounds. These procedures are illustrated by the following representative processes
20 in which the various groups and radicals such as G¹, G², A, B, X¹, Ar¹ and Q are as hereinbefore defined (unless stated otherwise), and are provided as a further feature of the present invention. In cases where the compounds contain a group such as an amino, hydroxy, or carboxy group, this group may be protected using a conventional protecting group which may be removed when desired by conventional means.

25 (a) For the production of those compounds of the formula I wherein T is N and X¹ is CO, the reaction, conveniently in the presence of a suitable base, of an amine of the formula II,



with an acid of the formula III.

5



III

or a reactive derivative thereof.

A suitable reactive derivative of an acid of the formula III is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid with a chloroformate such as isobutyl chloroformate or with an activated ketone such as 1,1'-carbonyldiimidazole; an active ester, for example an ester formed by the reaction of the acid and a phenol such as pentafluorophenol, an ester such as pentafluorophenyl trifluoroacetate or an alcohol such as N-hydroxybenzotriazole or
15 N-hydroxysuccinimide; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as N,N-dicyclohexylcarbodiimide or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide.

20 The reaction is conveniently carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example *n*-butyl-lithium, or a
25 dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide,
30 N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxy carbonyl, ethoxy carbonyl or tert-butoxy carbonyl group, an arylmethoxy carbonyl group, for example benzyloxy carbonyl, or an aroyl group, for example benzoyl. The
5 deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a tert-butoxy carbonyl group may be removed, for example, by
10 treatment with a suitable acid such as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxy carbonyl group such as a benzyloxy carbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is,
15 for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

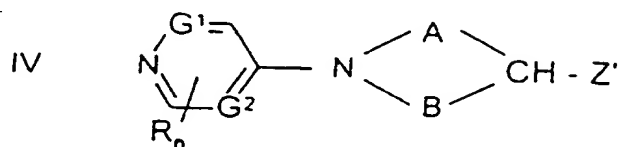
A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting
20 groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

25 A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a tert-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by
30 hydrogenation over a catalyst such as palladium-on-carbon.

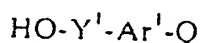
An analogous procedure may be used for those compounds of formula I wherein X^1 is a group of the formula SO or SO₂.

- (b) For the production of those compounds of the formula I wherein T is CH and X¹ is O the reaction, conveniently in the presence of a suitable coupling agent, of a compound of the formula IV.

5



10 wherein Z' is a displaceable group, with a compound of the formula V.



V

A suitable value for the displaceable group Z' is, for example, a halogeno or sulphonyloxy group, for example a fluoro, chloro, bromo, mesyloxy or 4-tolylsulphonyloxy group.

A suitable reagent for the coupling reaction when Z' is a halogeno or sulphonyloxy group is, for example, a suitable base, for example, an alkali or alkaline earth metal carbonate, hydroxide or hydride, for example sodium carbonate, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride. The alkylation reaction is preferably performed in a suitable inert solvent or diluent, for example N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetone, 1,2-dimethoxyethane or tetrahydrofuran, and at a temperature in the range, for example, -10° to 150°C, conveniently at or near ambient temperature.

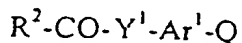
Alternatively, the displaceable group Z' is provided in place of the HO-group in the compound of formula V and the HO-group is provided in place of the displaceable group Z' in the compound of formula IV.

A suitable reagent for the coupling reaction of the alcohol of the formula IV wherein Z is a hydroxy group is, for example, the reagent obtained when said alcohol is reacted with a di-(1-4C)alkyl azodicarboxylate in the presence of a triarylphosphine or tri-(1-4C)alkylphosphine, for example with diethyl azodicarboxylate in the presence of triphenylphosphine or tributylphosphine. The reaction is preferably performed in a suitable inert solvent or diluent, for example acetone, 1,2-dimethoxyethane or tetrahydrofuran, and at a temperature in the range, for example, 10° to 80°C, conveniently at or near ambient temperature.

An analogous procedure may be employed for the preparation of those compounds of the formula I wherein T is CH and X¹ is a group of the formula S.

(c) For the production of those compounds of the formula I wherein T¹ is N and X¹ is CH(R²), the reductive amination of a keto compound of the formula VI,

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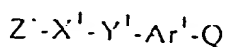


VI

with an amine of the formula II.

Any reducing agent known in the art for promoting a reductive amination reaction may be employed. A suitable reducing agent is, for example, a hydride reducing agent, for example an alkali metal aluminium hydride such as lithium aluminium hydride or, preferably, an alkali metal borohydride such as sodium borohydride, sodium cyanoborohydride, sodium triethylborohydride, sodium trimethoxyborohydride and sodium triacetoxyborohydride. The reaction is conveniently performed in a suitable inert solvent or diluent, for example tetrahydrofuran and diethyl ether for the more powerful reducing agents such as lithium aluminium hydride, and, for example, methylene chloride or a protic solvent such as methanol and ethanol for the less powerful reducing agents such as sodium triacetoxyborohydride. The reaction is performed at a temperature in the range, for example, 10° to 80°C, conveniently at or near ambient temperature.

30 (d) The reaction of an amine of formula II with a compound of formula VII,

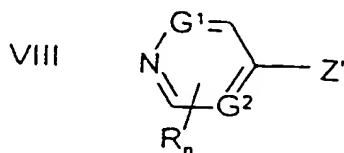


XI

wherein Z' is a displaceable group as defined hereinbefore. The reaction may be performed, for example, in the presence of a catalytic amount of sodium hydride. The reaction is conveniently performed in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0° to 150°C . conveniently at or near ambient temperature.

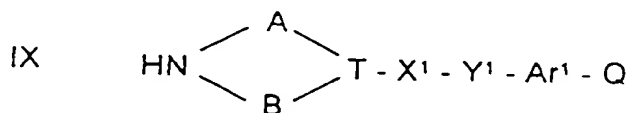
(e) The reaction of a compound of formula VIII

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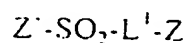
wherein Z' is a displaceable group as defined herein before with a compound of formula IX

15



The reaction is conveniently performed in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0° to 150°C . conveniently at or near ambient temperature.

(f) For the production of those compounds of the formula I wherein X^2 is a group of the formula $\text{NR}^{10}\text{SO}_2$, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of an amine of the formula X, with a compound of the formula XI,



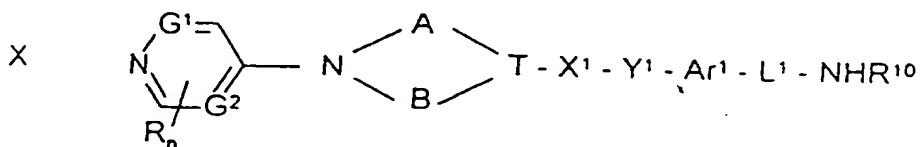
XI

wherein Z' is a displaceable group as defined hereinbefore.

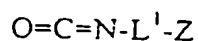
The reaction is conveniently performed in a suitable inert solvent or diluent⁴ as defined hereinbefore and at a temperature in the range, for example, 0° to 150°C, conveniently at or near ambient temperature.

5 An analogous procedure may be employed for those compounds of the formula I wherein X² is a group of the formula NR¹²CO.

(g) For the production of those compounds of the formula I wherein X² is a group of the formula NR¹³CONR¹⁴, the reaction, conveniently in the presence of a suitable base as
10 defined hereinbefore, of an amine of the formula X,



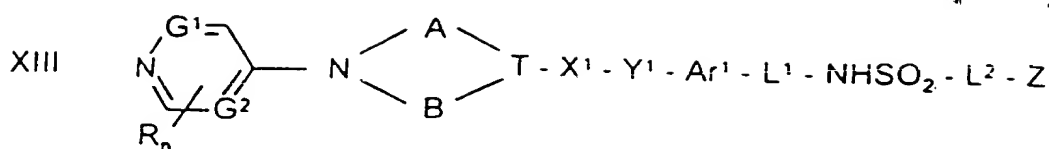
15 with a compound of the formula XII,



XII

The reaction is conveniently performed in a suitable inert solvent or diluent as
20 defined hereinbefore and at a temperature in the range, for example, 0° to 150°C, conveniently at or near ambient temperature.

(h) For the production of those compounds of the formula I wherein X² is a group of the formula NR¹⁰SO₂ and R¹⁰ represents (1-4C)alkyl, the reaction, conveniently in the presence
25 of a suitable base as defined hereinbefore, of a corresponding sulphonamide of the formula XIII.



with a compound of the formula XIV,

5



XIV

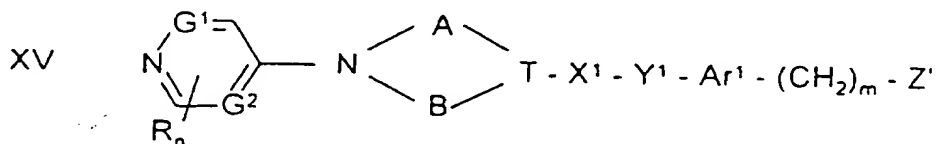
wherein Z' is a displaceable group as defined hereinbefore.

The reaction is conveniently performed in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0° to 150°C .

10 conveniently at or near ambient temperature.

An analogous procedure may be employed for those compounds of the formula I wherein X^2 is a group of the formula $\text{SO}_2\text{NR}^{11}$ or NR^{12}CO .

(i) For the production of those compounds of the formula I wherein L^1 represents (1-
15 4C)alkylene and X^2 is S, the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a compound of the formula XV,



20

wherein m is 1, 2, 3 or 4, and Z' is a displaceable group as defined hereinbefore with a thiol of the formula XVI,



XVI

25

The reaction is conveniently performed in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0° to 150°C , conveniently at or near ambient temperature.

(j) For the production of those compounds of the formula I wherein Ar¹ or Z bears a carboxy or carboxy-containing group, the hydrolysis of a compound of the formula I wherein Ar¹ or Z bears a (1-6C)alkoxycarbonyl group.

5 The hydrolysis reaction may conveniently be carried out in a conventional manner using, for example, acidic or basic catalysis. A suitable acid for the acidic hydrolysis of an ester group is, for example, an inorganic acid such as hydrochloric or sulphuric acid. A suitable base for the basic hydrolysis of an ester group is, for example, an alkali or alkaline earth metal hydroxide such as sodium hydroxide or potassium hydroxide.

10 The reaction is conveniently performed in a suitable solvent or diluent such as an alcohol, for example methanol or ethanol, and at a temperature in the range, for example 0° to 120°C, conveniently in the range of 15° to 60°C.

(k) For the production of those compounds of the formula I wherein Ar¹ or Z bears a
15 carbamoyl, N-(1-6C)alkylcarbamoyl or alkyl-di-N[(1-6C)carbamoyl] group, the reaction of a compound of the formula I wherein Ar¹ or Z bears a carboxy group, or a reactive derivative thereof as defined hereinbefore, with ammonia or an appropriate alkylamine or dialkylamine.

The reaction is conveniently performed in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 0° to 120°C, conveniently in the
20 range 15° to 60°.

(l) For the production of those compounds of the formula I wherein X¹ is a group of the formula SO or SO₂ wherein Ar¹ or Z bears a (1-6C)alkylsulphinyl or (1-6C)alkylsulphonyl, substituent or wherein X² is a group of the formula SO or SO₂, the oxidation of the
25 corresponding compound of the formula I which contains a thio group.

A suitable oxidising agent is, for example, any agent known in the art for the oxidation of thio to sulphinyl and/or sulphonyl, for example, hydrogen peroxide, a peracid (such as 3-chloroperoxybenzoic or peroxyacetic acid), an alkali metal peroxysulphate (such as potassium peroxymonosulphate), chromium trioxide or gaseous oxygen in the presence of
30 platinum. The oxidation is generally carried out under as mild conditions as possible and with the required stoichiometric amount of oxidising agent in order to reduce the risk of over oxidation and damage to other functional groups. In general the reaction is carried out in a

suitable solvent or diluent such as methylene chloride, chloroform, acetone, tetrahydrofuran or tert-butyl methyl ether and at a temperature, for example, at or near ambient temperature, that is in the range 15 to 35°C. When a compound carrying a sulphinyl group is required a milder oxidising agent may also be used, for example sodium or potassium metaperiodate.

5 conveniently in a polar solvent such as acetic acid or ethanol. It will be appreciated that when a compound of the formula I containing a sulphonyl group is required, it may be obtained by oxidation of the corresponding sulphinyl compound as well as of the corresponding thio compound.

As mentioned above, it will be appreciated that in some of the reactions
10 mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein. Suitable protecting groups are mentioned under (a) above. The protecting
15 groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

It will also be appreciated that certain of the various optional substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or
20 immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic
25 substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acylhalide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications
30 include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

When a pharmaceutically-acceptable salt of a compound of the formula I is required, it may be obtained, for example, by reaction of said compound with the appropriate acid (which affords a physiologically acceptable anion), or with the appropriate base (which affords a physiologically acceptable cation), or by any other conventional salt formation procedure.

When an optically active form of a compound of the formula I is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically active starting material or by resolution of a racemic form of said compound using a conventional procedure. As mentioned previously, the compounds of the formula I (and their pharmaceutically-acceptable salts) are inhibitors of the enzyme oxido-squalene cyclase. Thus, the compounds of the present invention are capable of inhibiting cholesterol biosynthesis and hence in lowering cholesterol levels in blood plasma.

The beneficial pharmacological properties of the compounds of the present invention may be demonstrated using one or more of the following techniques.

(a) In vitro test to measure inhibition of oxido-squalene cyclase

This test measures the inhibition of microsomal oxido-squalene cyclase in vitro by compounds at set concentrations in the incubation medium.

Microsomes are prepared from rat liver according to methods known in the art, for example, the method described in published European Patent Application No 324,421 and stored in liquid nitrogen prior to assay. Assay vials are kept at 37°C throughout the incubation. The microsomes typically contain 15-20mg of protein per ml of microsomes. For assay, 1ml of microsomes are diluted by the addition of 722µl of 50mM phosphate buffer pH 7.4.

Phosphate buffered Tween 80 (polyoxyethylene sorbitan monolaurate) is prepared by adding 0.1g Tween 80 to 100ml of 50mM phosphate buffer.

A stock solution of oxido-squalene is made up as a solution in ethanol (0.65mg.ml⁻¹). 18µl of radio-labelled oxido-squalene (1µCi.ml⁻¹) is evaporated to dryness under a stream of nitrogen and redissolved in 1ml of ethanol and 1ml of the stock solution of oxido-squalene is added.

The test compound is dissolved in dimethyl sulphoxide to give a 10^{-4} M stock solution. Dilutions are made from the stock to give 10^{-5} M, 10^{-6} M etc.

Phosphate buffered Tween 80 (28 μ l) is placed in 5ml disposable plastic vials and 4 μ l of the solution of the test compound is added and mixed well. An aliquot of the oxido-squalene mix (15 μ l) is added and the vials pre-incubated for 10 minutes at 37°C. A portion of the microsomes (14.6 μ l) are then added and incubated for a further 1 hour. The reaction is stopped by the addition of 315 μ l of a mixture of 16% KOH in 20% ethanol.

The samples are then placed in a water bath at 80°C for 2 hours to saponify. At the end of this process water (630 μ l) is added followed by hexane (5ml). The samples are tumble mixed for 5 minutes and then centrifuged. The hexane phase is removed and evaporated under nitrogen. The samples are then reconstituted in 300 μ l of a 80:20 mixture of acetonitrile:isopropyl alcohol. The samples are then chromatographed using a Hichrom 30DS1 column with an isocratic elution using a 95:5 mixture of acetonitrile:isopropyl alcohol and a flow rate of 1ml.min⁻¹. The output from the UV detector is connected to a radio-chemical detector to visualise radiolabelled sterols. Reaction rate is measured as the conversion of oxido-squalene to lanosterol, and the effects of test compounds are expressed as an inhibition of this process.

By way of example, the compound described in Example 25 gave 100% inhibition at 1 μ M.

20 (b) In vivo test to measure inhibition of Oxido-Squalene Cyclase

The ability of a compound to inhibit oxido-squalene cyclase and/or inhibit cholesterol biosynthesis may be assessed by a routine laboratory procedure carried out in the rat. The test involves administration of the compound to rats on a reversed lighting regimen. Female rats (35 - 55g) are housed in reverse lighting conditions (red light from 0200h - 1400h) for a period of about 2 weeks prior to test. Animals are allowed free access to chow and drinking water throughout this period. At test, animals should weigh 100 - 140g. The rats are dosed orally with the compound (typically 10-50mg/kg) formulated in a polyethylene glycol/hydroxypropylmethyl cellulose mix. After 1 hour the rats are given tritiated sodium mevalonate (15 μ Ci/kg) intraperitoneally. Two hours after administration of the compound the rats are terminated and a piece of liver removed and weighed. The tissue is saponified at 80°C for 2 hours in an ethanolic/potassium hydroxide solution (80% w/v

aqueous KOH diluted 1:10 with ethanol). Water (2ml) is added and the mixture extracted with iso²hexane (2 x 5ml). The organic extracts are combined, evaporated to dryness under a stream of nitrogen and the residue is dissolved in a mixture of acetonitrile/iso-propanol (300μl). An aliquot (200μl) of this solution is loaded onto a HPLC column to separate the 5 sterols. The radio-label content of each fraction is assessed using a radio chemical flow detector. Inhibitors of oxido-squalene cyclase are classed as those compounds which caused a build up of substrate and a concomitant disappearance of cholesterol and its precursors. ED50 values are generated in the usual manner.

By way of example, the compound described in Example 18 below gave 59%
10 inhibition of cholesterol biosynthesis when dosed at 2mg/kg; and the compound described in Example 27 70% inhibition when dosed at 2mg/kg.

The compounds of the present invention are oxido-squalene cyclase inhibitors and hence possess the property of inhibiting cholesterol biosynthesis. Accordingly, there is also provided the use of a compound of formula I, or a pharmaceutically acceptable salt thereof,
15 (as hereinbefore defined) for the manufacture of a medicament for inhibiting cholesterol biosynthesis. The compound N-[4-[4-(4-pyridyl)piperazin-1-ylcarbonyl]phenyl](E)-4-chlorostyrenesulphonamide and its salts are included in this aspect of the present invention and the aspect which follow relating to uses of the compounds of the present invention. Thus the compounds of the present invention will be useful in treating diseases or medical
20 conditions in which an inhibition of oxido-squalene cyclase is desirable, for example those in which a lowering of the level of cholesterol in blood plasma is desirable.

In particular, the compounds of the present invention will be useful in treating hypercholesterolemia and hypertriglyceridaemia, and in the treatment of atherosclerotic vascular diseases such as atherosclerosis, coronary heart disease including myocardial
25 infarction, angina, stroke and peripheral vascular disease. Such uses may lead to a reduction of morbidity in patients with ischaemic heart disease, whether or not they have a medical history of coronary heart disease. Compounds of the invention may also have benefit in the treatment of dermatological conditions such as xanthomas and xanthelasmas and in the treatment of gallstones.

30 Thus according to a further feature of the present invention there is provided a method of inhibiting oxido-squalene cyclase in a warm-blooded animal (such as man) requiring such treatment, which method comprises administering to said animal an effective amount of a

compound of formula I (as herein defined), or a pharmaceutically-acceptable salt thereof. In particular, the present invention provides a method of inhibiting cholesterol biosynthesis, and more particularly to a method of treating hypercholesterolemia and atheromatous vascular degeneration (such as atherosclerosis).

5 Thus the present invention also provides the use of a compound of formula I (as herein defined), or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament for treating diseases or medical conditions in which a lowering of the level of cholesterol in blood plasma is desirable (such as hypercholesterolemia and atherosclerosis).

In particular, the compounds of the present invention are potentially useful in
10 inhibiting cholesterol biosynthesis in man and hence in treating the above-mentioned medical conditions in man.

When used in the treatment of diseases and medical conditions such as those mentioned above it is envisaged that a compound of formula I (or a pharmaceutically acceptable salt thereof) will be administered orally, intravenously, or by some other
15 medically acceptable route so that a dose in the general range of, for example, 0.01 to 10 mg per kg body weight is received. However it will be understood that the precise dose administered will necessarily vary according to the nature and severity of the disease, the age and sex of the patient being treated and the route of administration.

In general, the compounds of formula I (or a pharmaceutically-acceptable salt
20 thereof) will usually be administered in the form of a pharmaceutical composition, that is together with a pharmaceutically acceptable diluent or carrier, and such a composition is provided as a further feature of the present invention.

A pharmaceutical composition of the present invention may be in a variety of dosage forms. For example, it may be in the form of tablets, capsules, solutions or
25 suspensions for oral administration, in the form of a suppository for rectal administration; in the form of a sterile solution or suspension for parenteral administration such as by intravenous or intramuscular injection.

A composition may be obtained by conventional procedures using pharmaceutically acceptable diluents and carriers well known in the art. Tablets and capsules
30 for oral administration may conveniently be formed with a coating, such as an enteric coating

(for example, one based on cellulose acetate phthalate), to minimise dissolution of the active ingredient of formula I (or a pharmaceutically-acceptable salt thereof) in the stomach or to mask unpleasant taste.

The compounds of the present invention may, if desired, be administered together
5 with (or sequentially to) one or more other pharmacological agents known to be useful in the treatment of cardiovascular disease. for example, together with agents such as HMG-CoA reductase inhibitors, bile acid sequestrants, other hypocholesterolaemic agents such as fibrates, for example gemfibrozil, and drugs for the treatment of coronary heart disease.

As inhibitors of oxido-squalene cyclase, the compounds of the present invention
10 may also find utility as antifungal agents, and so the present invention also provides a method of inhibiting cholesterol biosynthesis in fungi. In particular the present invention provides a method of treating fungal infections which comprises administration to a warm blooded animal, such as man, in need of such treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof. When used in this way the compounds of the
15 present invention may, in addition to the formulations mentioned above, be adapted for topical administration and such a composition is provided as a further feature of the present invention. Such compositions may be in a variety of forms, for example creams or lotions.

Selected compounds of the invention having utility as antifungal agents are compounds of the formula I wherein

20 G^1 is CH,

G^2 is CH or N

R is as defined hereinbefore

n is 1 or 2

T is CH or N, when T is CH then X^1Y^1 together are O or S, when T is N then X^1Y^1 together
25 are a bond,

Ar^1 is a phenylene ring, a pyridyl ring, or a 9- or 10-membered bicyclic heteroaryl ring containing 1, 2, or 3 heteroatoms selected from nitrogen, oxygen and sulphur, and may optionally bear one or more substituents selected from halogeno, nitro, cyano, (1-6C) alkyl, (1-6C)alkylthio, halogeno(1-6C)alkyl, halogeno(1-6C)alkylthio, halogeno(1-6C)alkoxy, (1-
30 6C)alkoxycarbonyl.

Q is selected from hydrogen and a group of formula $L^1X^2L^2Z$ in which L^1 is a bond or (1-4C)alkylene. L^2 is a bond or (1-4C)alkylene. X^2 is a bond, NR^8 , O or S, in which R^8 is hydrogen or (1-4C) alkyl; and

Z is selected from phenyl, and a monocyclic heterocyclic moiety containing 1,2,3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur, and may optionally bear one or more substituents selected from halogeno, nitro, cyano, (1-6C) alkyl, (1-6C)alkylthio, halogeno(1-6C)alkyl, halogeno(1-6C)alkylthio, halogeno(1-6C)alkoxy, (1-6C)alkoxycarbonyl;

Further selected antifungal compounds are as above and wherein Ar^1 is a phenylene ring, a 2-pyridyl ring, a benzthiazol-2yl ring, a 2-quinoyloxy ring, a benzoxazolyl ring, a thiazolopyridin-2yl ring, or a quinoxalinyloxy ring. Further selected antifungal compounds are as above and wherein R is hydrogen, halogeno or (1-4C)alkyl. Further selected antifungal compounds are as above and wherein the substituent Q on Ar^1 is in the 4-position. Further selected antifungal compounds are as above and wherein the substituent(s) on Ar^1 and/or Z are independently selected from methyl, methylthio, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, chlorine, bromine, fluorine and methoxycarbonyl.

In a further aspect of the invention we claim the use of a compound as defined above as an antifungal agent. We also claim a method for inhibiting cholesterol biosynthesis in fungi which comprises the use of a compound as defined above.

In a further aspect of the invention we claim a pharmaceutical composition comprising one or more compounds as defined above for use in the treatment of fungal infections of the human or animal body.

The antifungal activity of the compounds of the invention may be determined in vitro in standard agar dilution tests and disc-diffusion tests and minimum inhibitory concentrations are obtained. Standard in vivo tests in mice are used to determine the effective dose of the test compounds in controlling systemic fungal infections.

By way of example the following test protocols may be used:

Primary in-vitro Screen

Compounds are formulated in DMSO at 2560 $\mu\text{g/ml}$ and diluted to four-times the top test concentration in a synthetic medium RPMI-1640. Serial 2-fold dilutions are prepared in microtitre plates and an equal volume of the inoculum added. Compounds are tested against 11 fungal species/strains including *Candida* spp., *Cryptococcus neoformans*, *Saccharomyces cerevisiae*, *Aspergillus fumigatus* and *Trichophyton quinckeianum*. The plates are incubated at

30°C, read by eye at 24h and then at 48h. MICs and IC₅₀s are determined from visual and multiscan (540nm) readings respectively.

Primary in-vivo screen

5 Mice are inoculated intravenously with a lethal challenge of *Candida albicans*. Groups of 4 mice are dosed with test compound at 0, 5 and 24h after infection. The health of the mice is monitored for 72h at which point the test is terminated. Untreated mice would be expected to die or be culled within 24h of infection. Activity is determined by increased survival of the treated group over that of control animals.

10

The invention will now be illustrated in the following Examples in which, unless otherwise stated:-

(i) evaporations were carried out by rotary evaporation in vacuo and work-up procedures were carried out after removal of residual solids by filtration;

15 (ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were generally performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck,

20 Darmstadt, Germany; alternatively high pressure liquid chromatography (HPLC) was performed on a Dynamax C-18 60A preparative reversed-phase column;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end-products of the formula I were confirmed by nuclear
25 magnetic resonance (NMR) and mass spectral techniques; unless otherwise stated, CD₃SOCD₃ solutions of the end-products of the formula I were used for the determination of NMR spectral data, chemical shift values were measured on the delta scale; the following abbreviations have been used; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet;

(vi) intermediates were not generally fully characterised and purity was assessed by
30 thin layer chromatographic, infra-red (IR) or NMR analysis;

(vii) melting points were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; melting points for the end-products of the formula I were

generally determined after crystallisation from a conventional organic solvent such as ethanol, methanol, acetone, ether or hexane, alone or in admixture; and

(viii) the following abbreviations have been used:-

- DMF N,N-dimethylformamide; THF tetrahydrofuran;
 5 DMSO dimethylsulphoxide; Et₃N triethylamine;
 CH₂Cl₂ dichloromethane; Na₂SO₄ sodium sulphate (anhydrous);
 K₂CO₃ potassium carbonate; NaOH sodium hydroxide;
 MeOH methanol; NH₄OH ammonium hydroxide;
 EtOAc ethyl acetate; ⁱPrNH₂ isopropylamine;
 10 Et₂O diethyl ether; MTBE methyl t-butyl ether;

'Column chromatography' refers to separation of components of a mixture by passage of a solution through a sinter filled with silica gel (230-400 mesh, E Merck, Darmstadt, Germany), with suction applied from beneath.

- 15 The starting materials are described below or are known materials. Many of the starting materials are commercially available. The following lists some of the commercially available starting materials:

Compound	Supplier
20 4-chloropyridine hydrochloride	Aldrich
3-hydroxypyrrolidine	Aldrich
(3R)-3-hydroxypyrrolidine	Fluorochem
4-hydroxypiperidine	Aldrich
2-bromo-5-trifluoromethylpyridine	Fluorochem
25 2-bromo-5-nitropyridine	Aldrich
2,5-dichloropyridine	Aldrich
2,5-dibromopyridine	Aldrich
2-bromo-5-methylpyridine	Aldrich
methyl 6-chloronicotinate	Lancaster
30 2-chloro-5-cyanopyridine	Avocado
2-chloro-3-nitro-4-methylpyridine	Aldrich
2,3-dichloropyridine	Aldrich

	2-bromo-5-nitropyridine	Aldrich
	2-chloroquinoline	Aldrich
	1-(4-pyridyl)piperazine	Emkachem
	2,3-dichloro-5-trifluoromethylpyridine	Aldrich
5	2,3,5-trichloropyridine	Fluka
	4-nitrobromobenzene	Aldrich
	4-chlorophenol	Aldrich
	4-(trifluoromethyloxy)phenol	Fluorochem
	4-methylmercaptophenol	Aldrich
10	4-trifluoromethylmercaptophenol	Fluorochem
	4-trifluoromethylphenol	Janssen
	4-bromophenol	Aldrich

Example 1

A solution of 4-toluenesulphonyl chloride (0.38g) in dichloromethane (25ml) was added dropwise to a stirred solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (536mg) in dichloromethane (50ml) containing triethylamine (0.5ml). The reaction mixture was stirred at ambient temperature overnight. The mixture was washed with aqueous sodium carbonate solution, water, brine, dried (MgSO_4) and evaporated. The residue was recrystallised from methanol to give 1-(4-pyridyl)-4-(4-toluenesulphonamidomethylphenyl)piperazine (0.36g) as a solid, m.p. 196-198 °C; microanalysis, found: C, 65.2; H, 6.2; N, 13.2%; $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_2\text{S}$ requires: C, 65.4; H, 6.2; N, 13.3%; NMR: 2.37(s, 3H), 3.15-3.3(m, 4H), 3.4-3.55(m, 4H), 3.81-3.88(d, 2H), 6.8-6.93(dd, 4H), 7.03-7.15 (d, 2H), 7.32-7.4(d, 2H), 7.6-7.7(d, 2H), 7.8-7.95(t, 1H), 8.1-8.2(d, 2H); MS: m/z 423 (MH)⁺.

The 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine used as starting material was prepared as follows:

A solution of N-(4-pyridyl)piperazine (9.78g), 4-fluorobenzonitrile (7.26g) and powdered potassium carbonate (10g) was stirred at 100 °C in DMSO (100ml) overnight. The solution was poured into water (500ml) to give a precipitate which was filtered and washed with water. The crude solid was dried in a vacuum oven overnight then dissolved in dichloromethane and purified by flash chromatography on alumina (ICN Alumina N 32-63) using an increasing concentration of ethyl acetate in dichloromethane (up to 100% ethyl acetate) as eluant. This gave a solid which was recrystallised from a mixture of ethyl acetate/isohexane to give 1-(4-cyanophenyl)-4-(4-pyridyl)piperazine (7.5g) as a solid, m.p. 157-158 °C; microanalysis, found: C, 72.7; H, 6.1; N, 21.0%; $\text{C}_{16}\text{H}_{16}\text{N}_4$ requires: C, 72.7; H, 6.1; N, 21.2%; NMR: 3.45-3.55(bs, 8H), 6.8-6.9(d, 2H), 7.0-7.1(d, 2H), 7.55-7.65(d, 2H), 8.1-8.2(d, 2H); MS: m/z 265 (MH)⁺.

A solution of 1-(4-cyanophenyl)-4-(4-pyridyl)piperazine (1.8g) in ethanol saturated with ammonia gas (150ml) was hydrogenated at 150 atmospheres and 100 °C (using Raney Nickel as catalyst) in a high pressure hydrogenation apparatus for 18 hours. The solution was filtered through diatomaceous earth and the filtrate evaporated to give a solid which was purified by flash chromatography on alumina (ICN Alumina N 32-63) using a mixture of 95:5 dichloromethane:methanol as eluant. The residue was recrystallised from tetrahydrofuran/isohexane to give 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (1.3g)

m.p. 168-170 °C; microanalysis, found: C, 71.5; H, 7.6; N, 20.5%; $C_{16}H_{20}N_4$ requires: C, 71.6; H, 7.5; N, 20.9%; NMR: 3.2-3.4(m, 4H), 3.4-3.6(m, 4H), 3.65(s, 2H), 6.8-6.9(d, 2H), 6.9-7.0(d, 2H), 7.15-7.25(d, 2H), 8.15-8.25(d, 2H); MS: m/z 269 (MH)⁺.

5 Example 2

4-Toluenesulphonyl chloride (95mg) was added to a solution of 1-(4-aminophenyl)-4-(4-pyridyl)piperazine (127mg) in dichloromethane (25ml) and the mixture was stirred at ambient temperature for 16 hours. The resulting precipitate was collected by filtration and washed with dichloromethane. There was thus obtained 1-(4-pyridyl)-4-[4-methylsulphonamido)phenyl]piperazine hydrochloride as a grey solid (160mg). mp. 293-294 °C; microanalysis, found: C, 59.4; H, 5.7; N, 12.6; $C_{22}H_{24}N_4O_2S \cdot HCl$ requires: C, 59.1; H, 5.8; N, 12.6; NMR: 2.35(s, 3H), 3.24(t, 4H), 3.81(t, 4H), 6.84(d, 2H), 6.96(d, 2H), 7.24(d, 2H), 7.33(d, 2H), 7.58(d, 2H), 8.26(d, 2H), 9.78(s, 1H), 13.45(broad, 1H); MS: m/z 409 (MH)⁺.

15 Example 3

4-Chlorostyrylsulphonyl chloride (118mg) in dichloromethane (5ml) was added to a solution of 1-(4-aminophenyl)-4-(4-pyridyl)piperazine (127mg) in dichloromethane (5ml) and stirred at ambient temperature for 2 hours. The resulting precipitate was collected by filtration, washed with dichloromethane then triturated with 10% methanol in dichloromethane. There was thus obtained (E)-1-(4-pyridyl)-4-[4-chlorostyrylsulphonamido]piperazine hydrochloride as a yellow solid (77mg). mp. 285-287 °C; microanalysis, found: C, 55.3; H, 4.6; N, 11.1; $C_{23}H_{23}ClN_4O_2S \cdot HCl \cdot \frac{1}{2}H_2O$ requires: C, 55.1; H, 4.8; N, 11.2; NMR: 3.24(m, 4H), 3.81(m, 4H), 6.92(d, 2H), 7.11(d, 2H), 7.20(d, 1H), 7.23(d, 2H), 7.33(d, 1H), 7.46(d, 2H), 7.71(d, 2H), 8.24(d, 2H), 9.65(s, 1H), 13.25(broad, 1H); MS: m/z 455 (MH)⁺.

25

Example 4

4-Dimethylamino-pyridine (30mg) and 4-bromophenylsulphonyl chloride (260mg) was added to a solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (268mg) in pyridine (5ml). The solution was heated on a steam bath for three hours. The solution was cooled to ambient temperature and evaporated. Water (100ml) was added to the residue and the solution acidified to pH 1 by addition of concentrated hydrochloric acid. The aqueous

solution was washed with ether (2x100ml) and then basified by addition of aqueous ammonia. The mixture was extracted with methylene chloride and the methylene chloride extracts were washed with water, brine, dried (MgSO_4) and evaporated. The residue was recrystallised from a mixture of ethyl acetate/tetrahydrofuran/isohexane to give 1-(4-pyridyl)-4-(4-bromophenylsulphonamidomethyl-phenyl)piperazine (155mg.) as a solid m.p. 180-182°C; microanalysis, found: C, 54.4; H, 4.8; N, 11.3%; $\text{C}_{22}\text{H}_{23}\text{BrN}_4\text{O}_2\text{S}$ requires: C, 54.2; H, 4.7; N, 11.5%; NMR: 3.15-3.3(m, 4H), 3.4-3.55(m, 4H), 3.85-3.95(d, 2H), 6.8-6.9(bm, 4H), 7.0-7.1(d, 2H), 7.6-7.8(q, 4H), 8.05-8.15(t, 2H), 8.18-8.25(bd, 1H); MS: m/z 487 (MH)⁺.

10 Example 5

4-Cyanophenylsulphonyl chloride (202mg) was added to a solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (268mg) in pyridine (20ml). The mixture was heated on a steam bath for three hours. The solvents were removed by evaporation and water (100ml) added to give a precipitate which was extracted into ethyl acetate (2x100ml). The ethyl acetate extracts were combined, washed with water, brine, dried (MgSO_4) - 10% methanol/methylene chloride as eluent to give a solid which was recrystallised from a mixture of tetrahydrofuran/methanol/isohexane to give 1-(4-pyridyl)-4-(4-cyanophenylsulphonamidomethyl-phenyl)piperazine (52mg) as a solid m.p. 229-230°C; microanalysis found: C, 62.8; H, 5.6; N, 15.7%; $\text{C}_{23}\text{H}_{23}\text{N}_5\text{O}_2\text{S} \cdot 0.25\text{H}_2\text{O}$ requires: C, 62.4; H, 5.4; N, 15.8%; NMR: 3.15-3.3(m, 4H), 3.4-3.55(m, 4H), 3.85-4.0(d, 2H), 6.8-6.9(dd, 4H), 7.0-7.1(d, 2H), 7.8-7.9(d, 2H), 7.95-8.05(d, 2H), 8.18-8.25(d, 2H), 8.25-8.4(bt, 1H); MS: m/z 434 (MH)⁺.

Example 6

4-Methoxybenzenesulphonyl chloride (0.25g) was dissolved in dry tetrahydrofuran (2.0ml) and treated with a warm solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (0.27g) in tetrahydrofuran (8.0ml) and triethylamine (0.2ml) in one portion. The reaction mixture was stirred overnight and then quenched by concentrating the reaction solution to a volume of 1ml followed by the addition of 1M solution of aq. NaHCO_3 (8ml). The mixture was stirred for 2 hours. The resulting precipitate was collected by filtration, washed with water and dried to give 1-(4-pyridyl)-4-(4-methoxyphenylsulphonamidomethyl-phenyl)piperazine (0.29g) as a solid m.p. 212-213°C; microanalysis found C, 62.9; H, 5.9;

N, 12.6%; $C_{23}H_{26}N_4O_3S$ requires C, 63.0; H, 5.98; N, 12.8%; NMR: 3.23(t, 4H), 3.47(t, 4H), 3.82(s, 3H), 3.89(d, 2H), 6.88(d, 4H), 7.07(m, 4H), 7.71(dd, 2H), 7.79(t, 1H), 8.18(bs, 2H); MS: m/z 439 (MH)⁺.

5 Example 7

A solution of 4-bromophenyl isocyanate (198mg) in tetrahydrofuran was added dropwise to a solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (268mg) in tetrahydrofuran (50ml). When the addition was complete, the solution was stirred at ambient temperature overnight. The precipitate was collected by filtration, filtered, washed with ether and recrystallised from methanol to give 1-(4-pyridyl)-4-(4-bromophenylureidomethyl-phenyl)piperazine (185mg) as a solid, m.p. 258-260°C; microanalysis found: C, 59.1; H, 5.3; N, 14.8%; $C_{23}H_{24}BrN_5O$ requires: C, 59.2; H, 5.2; N, 15.0%; NMR: 3.15-3.3(m, 4H), 3.4-3.55(m, 4H), 4.15-4.25(d, 2H), 6.45-6.55(t, 1H), 6.8-6.9(d, 2H), 6.9-7.0(d, 2H), 7.15-7.25(d, 2H), 7.38(s, 4H), 8.18-8.25(d, 2H), 8.6(bs, 1H); MS: m/z 466 (MH)⁺.

15

Example 8

A solution of 4-cyanophenyl isocyanate (144mg) in tetrahydrofuran was added dropwise to a solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (268mg) in tetrahydrofuran (50ml). When the addition was complete, the solution was stirred at ambient temperature overnight. The precipitate was collected by filtration, washed with ether and recrystallised from a mixture of tetrahydrofuran/methanol/isohexane to give 1-(4-pyridyl)-4-(4-cyanophenylureidomethyl-phenyl)piperazine (52mg) as a solid, m.p. 254-255°C; microanalysis, found: C, 69.5; H, 6.0; N, 20.1%; $C_{24}H_{24}N_6O$ requires: C, 69.9; H, 5.9; N, 20.4%; NMR: 3.15-3.3(m, 4H), 3.4-3.55(m, 4H), 4.15-4.25(d, 2H), 6.65-6.75(t, 1H), 6.80-6.90(d, 2H), 6.90-7.00(d, 2H), 7.15-7.25(d, 2H), 7.50-7.70(q, 4H), 8.18-8.25(d, 2H), 9.0(bs, 1H); MS: m/z 413 (MH)⁺.

25

Example 9

A solution of 4-bromobenzoyl chloride (240mg) in dichloromethane (10ml) was added dropwise to a stirred solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (268mg) in dichloromethane (50ml) containing triethylamine (0.5ml). The resulting solution was stirred at ambient temperature for three hours. The solution was poured into water and the solid which

precipitated was collected by filtration and washed with water, acetone and recrystallised from methanol to give 1-(4-pyridyl)-4-(4-bromobenzoylamido-methylphenyl)piperazine (230mg) as a solid. microanalysis. found: C.61.3; H.5.2; N.11.9%; $C_{23}H_{23}BrN_4O$ requires: C.61.2; H.5.14; N.12.4%; NMR: 3.15-3.3(m,4H), 3.4-3.55(m,4H), 4.35-4.45(d,2H), 6.8-6.93(bm,2H), 6.90-7.00(d,2H), 7.15-7.25(d,2H), 7.6-7.7(d,2H), 7.75-7.85(d,2H), 8.10-8.25(b,2H), 8.90-9.00(bt,1H); MS: m/z 451 (MH)⁺.

Example 10

A solution of methanesulphonyl chloride (0.155ml) in dichloromethane (10ml) was added dropwise to a stirred solution of 1-(4-aminomethylphenyl)-4-(4-pyridyl)piperazine (536mg) in dichloromethane (50ml) containing triethylamine (0.5ml). The resulting solution was stirred at ambient temperature for 7 hours. The solution was evaporated and the residue was extracted with ethyl acetate. The ethyl acetate extracts were washed with water, sodium bicarbonate solution, brine, dried ($MgSO_4$) and evaporated. The solid residue was recrystallised from methanol to give 1-(4-pyridyl)-4-(methanesulphonamido-methylphenyl)piperazine (356mg) as a solid, m.p.236-238°C; microanalysis found: C.59.3; H.6.4; N.16.2%; $C_{17}H_{22}N_4O_2S$ requires: C,58.8; H,6.4; N,16.2%; NMR: 2.8(s,3H), 3.15-3.3(m,4H), 3.4-3.55(m,4H), 4.00-4.10(d,2H), 6.80-6.90(d,2H), 6.90-7.00(d,2H), 7.15-7.25(d,2H), 7.3-7.5(t,1H), 8.20(d,1H); MS: m/z 311 (MH)⁺.

20

Example 11

Sodium hydride (55mg) (50% dispersion in oil) was added to a stirred solution of 1-(4-pyridyl)-4-(4-toluenesulphonamidomethyl-phenyl)piperazine (422mg) in dimethyl formamide (20ml) under argon. The solution was stirred at 70-80°C for 1 hour. The solution was cooled to ambient temperature and a solution of methyl iodide (150mg) in dimethyl formamide (1ml) was added dropwise. When the addition was complete, the solution was stirred at ambient temperature for 4 hours. Water (120ml) was added and the solution extracted with hot ethyl acetate (2x100ml). The combined extracts were washed with water, brine, dried ($MgSO_4$) and evaporated. A solid residue was recrystallised from a mixture of ethyl acetate/isohexane to give 1-(4-pyridyl)-4-(4-toluenesulphonamethylamidomethyl-phenyl)piperazine (65mg) as a solid, m.p. 183-185°C; microanalysis. found: C.65.7; H.6.5; N.12.3%; $C_{24}H_{28}N_4O_2S$ requires:

C,66.0; H,6.46; N,12.8%; NMR: 2.43(s,3H), 3.2-3.35(m,4H), 3.4-3.55(m,4H), 4.0(s,2H), 6.9-7.0(d,2H), 7.1-7.2(d,2H), 7.4-7.5(d,2H), 7.7-7.8(d,2H); MS: m/z 437 (MH)⁺.

Example 12

5 Triethylamine (0.43ml) was added to a stirred suspension of 1-(4-anilinocarboxy)-4-(4-pyridyl)piperazine hydrochloride (356mg) in dry DMF (4ml). After 1 hour, 4-methylbenzenesulphonylchloride (210mg) was added and stirring continued for 16 hours. The reaction mixture was diluted with dichloromethane (25ml) and washed with water (2 x 7ml), saturated brine (7ml), dried (MgSO₄) and evaporated. The resulting oil, was purified by
10 flash chromatography on silica gel using an increasing polar mixture of 2 to 10% v/v methanol in dichloromethane as eluant to give 1-(4-pyridyl)-4-(4-toluenesulphonamido-benzoyl)piperazine (94mg), as a solid, m.p. 139-141°C; microanalysis, found: C, 61.5; H, 5.9; N, 12.4%; C₂₃H₂₄N₄O₃S.0.5H₂O requires: C,61.9; H,5.6; N,12.6%; NMR: 2.34(3H,s), 3.40(4H,m), 3.57(4H,m), 6.80(2H,d), 7.14(2H,d), 7.33(4H,m), 7.70(2H,d), 8.18(2H,d),
15 10.55(1H,bs); MS: m/z 437 (MH)⁺.

The 1-(4-anilinocarboxy)-4-(4-pyridyl)piperazine hydrochloride used as starting material was prepared as follows:

10% w/w Palladium on charcoal (200mg) was added to a solution of 1-(4-nitrobenzenecarboxy)-4-(4-pyridyl)piperazine (936mg) in a mixture of dichloromethane
20 (25ml) and methanol (10ml) containing 4.55M hydrogen chloride in dry ether (1.3ml). The mixture was hydrogenated at ambient temperature and pressure until the theoretical amount of hydrogen had been taken up. The mixture was filtered through diatomaceous earth and the filtrate evaporated. Trituration of the resulting solid with ether gave 1-(4-anilinocarboxy)-4-(4-pyridyl)piperazine dihydrochloride (980mg) as a pale yellow solid, m.p. >350°C;
25 microanalysis, found: C,54.1; H,5.8; N,15.7%; C₁₆H₁₈N₄O.2HCl requires: C,54.1; H,5.7; N,15.8%; NMR: 3.67(4H,m), 3.78(4H,m), 3.3 to 4.5 (b), 6.97(2H,d), 7.19(2H,d), 7.37(2H,d), 8.29(2H,d); MS: m/z 283 (MH)⁺.

Example 13

30 To a stirred cooled (0°C) solution of 4-(naphthalene-2-sulphonyl)benzoic acid (312mg) in DMF (4ml), was added 1,1'-carbonyldiimidazole (162mg). The mixture was

stirred at 0°C for 30 minutes and then N-(4-pyridyl)piperazine (163mg) was added. The cooling bath was removed and the mixture was stirred at room temperature overnight. The solvent was removed by evaporation under high vacuum. The residue was dissolved in a mixture of ethyl acetate and water. The ethyl acetate extract was dried (MgSO₄) and
5 evaporated to give a solid residue (170mg), which was recrystallised from a mixture of methanol, ethyl acetate and isohexane to afford 1-(4-pyridyl)-4-(4-naphthalene-2-sulphonyl)benzoyl)piperazine (124mg) as white needles. NMR: 3.25-3.5(m,6H); 3.6-3.9(m,2H); 6.8(d,2H); 7.7(d,2H); 7.77(dd,1H); 7.95(dd,1H); 8.05-8.25(m,8H); 8.77(d,1H); microanalysis: found C,63.5; H,5.5; N,8.5%; C₂₆H₂₃N₃O₃S.2H₂O requires C,63.5; H,5.5;
10 N,8.6; MS: m/z 457 (MH)⁺.

The 4-(naphthalene-2-sulphonyl)-benzoic acid used as starting material was prepared as follows:

4-(Naphthalene-2-sulphonyl)benzaldehyde (0.97g) was suspended in water (25ml) containing cetyltrimethylammonium bromide (58mg). The mixture was stirred and heated to
15 60°C, and potassium permanganate (0.95g) was added in small portions over 1 hour. Heating was continued for a further 2 hours. The mixture was cooled to room temperature and was acidified with 2M hydrochloric acid. Ethyl acetate was added to the stirred mixture, which was filtered through a pad of celite. The ethyl acetate layer was washed with brine, dried (MgSO₄), and evaporated to afford 4-(naphthalene-2-sulphonyl)benzoic acid (0.42g) as solid
20 residue; NMR: 7.7(dd,1H); 7.95(dd,1H); 8.1-8.2(m,8H); 8.7(d,1H); microanalysis: found; C,58.6; H,3.9%; C₁₇H₁₂O₄S.2H₂O requires: C,58.6; H,4.6%; MS: m/z 312(MH)⁺.

Example 14

Carbonyl diimidazole (340mg) was added to a solution of 4-benzoylbenzoic acid
25 (440mg) in dimethylformamide (10ml). After stirring at ambient temperature for 45 minutes, N-(4-pyridyl)piperazine (326mg) was added as a solid, in one portion and stirring continued at ambient temperature overnight. The reaction mixture was poured into water (50ml) and extracted with ethyl acetate (3 x 20ml). The extracts were combined, washed with water, brine, dried (MgSO₄) and evaporated to give a solid which was purified by recrystallisation
30 from a mixture of ethyl acetate, methanol and hexane (10/3/9) to give 1-(4-pyridyl)-4-(4-benzoyl-benzoyl)piperazine as pale yellow crystals (660mg), m.p. 153-154°C; microanalysis.

found: C, 74.5; H, 5.6; N, 11.3%; $C_{23}H_{21}N_3O_2$ requires: C, 74.4; H, 5.7; N, 11.3%; NMR: 3.3-3.9(m, 8H), 6.9(d, 2H), 7.5-7.9(m, 9H), 8.2(d, 2H); MS: m/z 372 (MH)⁺.

Example 15

- 5 To a solution of 4-phenoxybenzaldehyde (198mg) in dichloromethane (20ml), N-(4-pyridyl)piperazine (163mg) and acetic acid (240mg) were added. The mixture was stirred at ambient temperature for 30 mins. and then sodium triacetoxyborohydride (318mg) was added in one portion. Stirring was continued at ambient temperature overnight. The reaction mixture was poured into 1M hydrochloric acid (50ml) and washed with ethyl acetate (50ml).
- 10 The aqueous layer was made basic with 2M sodium hydroxide solution and extracted with dichloromethane (2 x 25ml). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give a white solid which was purified by chromatography on silica gel (Mega Bond Elut column) using an increasing concentration of methanol in dichloromethane (up to 4% methanol) as eluant to give 1-(4-pyridyl)-4-(4-phenoxy-phenyl)piperazine (168mg)
- 15 as a solid: microanalysis, found: C, 76.5; H, 6.6; N, 11.9%; $C_{23}H_{23}N_3O$ requires: C, 76.5; H, 6.7; N, 12.2%; NMR: 3.2-3.45(m, 8H); 3.5(s, 2H); 6.8(d, 2H); 6.9-7.05(m, 4H); 7.1-7.2(m, 1H); 7.25-7.45(m, 4H); 8.1(d, 2H); MS: m/z 345 (MH)⁺.

Example 16

- 20 A solution of N-(4-pyridyl)piperazine (0.33g) in dry dimethylformamide (15ml) was treated with sodium hydride (0.14g) (45-55% dispersion in oil). The reaction mixture was then stirred for 45 minutes at ambient temperature under argon. 4-Bromobenzyl bromide (0.58g) was added and the mixture heated slowly to 60°C and then maintained at this temperature for 2 hours. The resulting mixture was then poured into water, basified with
- 25 aq. $NaHCO_3$ solution and then extracted with diethyl ether. The organic extracts were then washed with aq. $NaHCO_3$, water, brine, dried (Na_2SO_4) and evaporated. The residue was recrystallised from acetonitrile to give 1-(4-pyridyl)-4-(4-bromobenzyl)piperazine (0.2g) as a solid, m.p. 140-141°C; microanalysis, found: C, 55.3; H, 5.2; N, 12.0%; $C_{16}H_{18}N_3Br$ requires: C, 55.4; H, 5.7; N, 12.1%; NMR: ($CDCl_3$) 2.54(t, 4H); 3.32(t, 4H); 3.51(s, 2H); 6.66(d, 2H);
- 30 7.23(d, 2H); 7.46(d, 2H); 8.29(d, 2H); MS: m/z 332 (MH)⁺.

Example 17

A solution of N-(4-pyridyl)piperazine (0.33g) in dry dimethylformamide (15ml) was treated with sodium hydride (0.14g) (45-55% dispersion in oil). The reaction mixture was then stirred for 30 minutes at ambient temperature under argon. 4-Cyanobenzyl bromide (0.41g) was added and the mixture heated slowly to 80°C and then maintained at this temperature for 2 hours. The resulting mixture was then poured into water, basified with aq. NaHCO₃ solution and then extracted with diethyl ether. The organic extracts were then washed with aq. NaHCO₃, water, brine, dried (MgSO₄) and evaporated. The residue was recrystallised from toluene/hexane to give 1-(4-pyridyl)-4-(4-cyanobenzyl)piperazine (0.08g) as a solid, m.p. 137-138°C; microanalysis, found: C, 73.3; H, 6.5; N, 19.8%; C₁₇H₁₈N₄ requires: C, 73.4; H, 6.5; N, 20.1%; NMR: (CDCl₃) 2.56(t,4H); 3.35(t,4H); 3.61(s,2H); 6.67(dd,2H); 7.49(d,2H); 7.63(d,2H); 8.28(dd,2H); MS: m/z 279(MH)⁺.

Example 18

A solution of N-(4-pyridyl)piperazine (0.33g) in dry dimethylformamide (15ml) was treated with sodium hydride (0.14g) (45-55% dispersion in oil). The reaction mixture was then stirred for 30 minutes at ambient temperature under argon. A solution of 2-fluoro-4-bromobenzyl bromide (2.6ml) (20% w/v in dichlorobenzene) was added and the mixture was heated slowly to 70°C and then maintained at this temperature for 24 hours. The resulting mixture was then poured into water and then extracted with diethyl ether. The organic extracts were then washed with aq. NaHCO₃, water, brine, dried (Na₂SO₄) and evaporated. The residue was then purified by flash chromatography on alumina (ICN Alumina N 32-63) using an increasing concentration of ethyl acetate in isohexane (50 - 100% ethyl acetate) and then up to 10% methanol in ethyl acetate as eluent to give after recrystallisation 1-(4-pyridyl)-4-(2-fluoro-4-bromobenzyl)piperazine (0.08g) as a solid, m.p. 77-78°C; microanalysis, found: C, 54.4; H, 4.8; N, 11.1%; C₁₆H₁₇N₃Br requires: C, 54.9; H, 4.9; N, 12.0%; NMR: 3.28(s,8H); 3.54(s,2H); 6.79(d,2H); 7.41(d,2H); 7.52(d,1H); 8.13(d,2H); MS: m/z 350 (MH)⁺.

Example 19

Using an analogous procedure to that described in Example 16, but using 3,4-dichlorobenzyl bromide as starting material was prepared 1-pyridyl-4-(3,4-dichlorobenzyl)piperazine (43% yield), microanalysis, found: C, 59.3; H, 5.4; N, 12.75%;

$C_{16}H_{17}Cl_2N_3$ requires C, 59.6; H, 5.3; N, 13.0%; NMR: 2.4-2.45 (m, 4H), 3.3-3.45 (m, 4H), 3.55 (s, 2H), 6.6 (d, 2H), 7.3-7.4 (dd, 1H), 7.55-7.65 (m, 2H), 8.15 (d, 2H); MS m/z 322 (MH)⁺.

Example 20

5 Using an analogous procedure to that described in Example 16, but using 4-nitrobenzylbromide as starting material, was prepared 1-pyridyl-4-(4-nitrobenzyl)piperazine (47% yield), NMR: 3.7 (s, 2H), 6.8 (d, 2H), 7.65 (d, 2H), 8.15 (d, 2H), 8.2 (d, 2H); MS: m/z 299 (MH)⁺.

10 Example 21

1-(4-Pyridyl)piperazine (9.78g) and 1-bromo-4-nitrobenzene (6.67g) were stirred as a melt at 120°C for 1 hour. The mixture was cooled to ambient temperature and 5% methanol in dichloromethane (100ml) was added. The solid mass broken up by sonication and the mixture was stirred for 16 hours. The resulting solid was collected by filtration and purified
15 by flash chromatography on silica gel using a gradient of 5-15% methanol / 0.1% ammonia (SG, 0.88) in dichloromethane as eluant to give a product of sufficient purity to continue (6.35g) m.p. 225-226°C.

A solution of this solid (1.0g) in concentrated hydrochloric acid (10ml) was treated with granulated zinc (0.5g) and stirred at 110°C for 2 hours. Water (50ml) was added to the
20 mixture and unreacted zinc was removed by filtration. The product hydrochloride precipitated from the filtrate on cooling. This solid was collected, dissolved in 20% potassium hydroxide, extracted with dichloromethane (4x 25ml), washed with water, brine, dried (MgSO₄) and evaporated. There was thus obtained 1-(4-aminophenyl)-4-(4-pyridyl)piperazine as a free base (0.88g), microanalysis, found: C, 70.8; H, 7.1; N, 22.0; $C_{15}H_{18}N_4$ requires: C, 71.0;
25 H, 7.3; N, 22.0; NMR: 3.01 (t, 4H), 3.41 (t, 4H), 6.52 (d, 2H), 6.75 (d, 2H), 6.86 (d, 2H), 8.17 (d, 2H); MS: m/z 255 (MH)⁺.

Example 22

A solution of 1-(4-pyridyl)piperazine (0.49g) in dry dichloromethane (20ml) and
30 triethylamine (0.7ml) was treated slowly with a solution of 4-bromobenzoyl chloride (0.7g) in dry dichloromethane (10ml). The reaction mixture was then stirred under argon for 2 hours.

The dichloromethane solvent was removed by evaporation and the residue dissolved in ethyl acetate. The organic extracts were then washed with aqueous sodium hydrogen carbonate solution, water, brine, dried (Na_2SO_4) and evaporated to yield a colourless oil. The residual oil was then triturated with diethyl ether and recrystallised from ethyl acetate/isohexane to give 1-(4-pyridyl)-4-(4-bromobenzoyl)piperazine (0.62g) as a solid, m.p. 128-129 °C; microanalysis, found: C, 55.7; H, 4.7; N, 12.0%; $\text{C}_{16}\text{H}_{16}\text{N}_2\text{OBr}$ requires: C, 55.5; H, 4.7; N, 12.1%; NMR: (CDCl_3) 3.36(s, 4H), 3.73(s, 4H), 6.67(dd, 2H), 7.33(dd, 2H), 7.58(dd, 2H), 8.34(dd, 2H); MS: m/z 346 (MH)⁺.

10 Example 23

A solution of 1-(4-pyridyl)piperazine (0.49g) in dry dichloromethane (20ml) and triethylamine (0.7ml) was treated slowly with a solution of 4-cyanobenzoyl chloride (0.50g) in dry dichloromethane (30ml). The reaction mixture was then stirred under argon for 2 hours. The dichloromethane solvent was removed by evaporation and the residue dissolved in ethyl acetate. The organic extracts were then washed with aqueous sodium hydrogen carbonate solution, water, brine, dried (Na_2SO_4) and evaporated to give a colourless oil which was crystallised from ethyl acetate/isohexane to afford 1-(4-pyridyl)-4-(4-cyanobenzoyl)piperazine (0.25g) as a solid, m.p. 164-165 °C; microanalysis, found: C, 69.7; H, 5.6; N, 18.5%; $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$ requires: C, 69.8; H, 5.52; N, 19.2%; NMR: (CDCl_3) 3.38(bs, 4H), 3.75(bs, 4H), 6.67(dd, 2H), 7.56(dd, 2H), 7.76(dd, 2H), 8.32(dd, 2H); MS: m/z 293 (MH)⁺.

Example 24

A solution of 2-fluoro-4-bromobenzoic acid (0.24g) in dry dimethylformamide (10ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.17g) and stirred for 30 minutes at ambient temperature under argon. A solution of 1-(4-pyridyl)piperazine (1.6g) in dry dimethylformamide (3ml) was added to the mixture and the mixture cooled to 50°C. The reaction was then allowed to warm to room temperature and stirred overnight. The solution was poured into water and then extracted into diethyl ether, washed with aqueous sodium hydrogen carbonate solution, water, brine, dried (Na_2SO_4) and evaporated to yield a colourless oil. This oil was then triturated with diethyl ether and recrystallised from ethyl acetate/isohexane to give 1-(4-pyridyl)-4-(2-fluoro-4-bromobenzoyl)piperazine (0.14g) as a solid, m.p. 125-126°C; microanalysis, found: C, 52.6;

H, 4.1; N, 11.2%; $C_{16}H_{15}BrFN_3O$ requires: C, 52.8; H, 4.15; N, 11.5%; NMR: ($CDCl_3$) 3.32(t, 2H), 3.46(t, 4H), 3.94(t, 2H), 6.68(dd, 2H), 7.29-7.43(m, 3H), 8.33(d, 2H); MS: m/z 364 (MH)⁺.

5 Example 25

A solution of 1-(4-pyridyl)piperazine (0.49g) and triethylamine (0.7ml) in dry dichloromethane (20ml) was treated slowly with a solution of 4-bromophenylsulphonyl chloride (0.77g) in dry dichloromethane (10ml). The reaction mixture was then stirred under argon for 2 hours. The dichloromethane solvent was removed by evaporation and the residue dissolved in ethyl acetate. The organic extracts were washed with water, brine, dried ($MgSO_4$) and evaporated to yield a white crystalline solid which was recrystallised from ethyl acetate to give 1-(4-pyridyl)-4-(4-bromophenylsulphonyl)piperazine (0.84g) as a solid, m.p. 199-200 °C; microanalysis, found: C, 47.3; H, 4.1; N, 10.9%; $C_{15}H_{16}BrN_3O_2S$ requires: C, 47.1; H, 4.22; N, 11.0%; NMR: ($CDCl_3$) 3.13(t, 4H), 3.42(t, 4H), 6.62(dd, 2H), 7.67(q, 4H), 8.29(d, 2H); MS: m/z 382 (MH)⁺.

Example 26

Pyridine (1ml) was added to a solution of 1-(4-pyridyl)piperazine (0.33g) in dry dichloromethane (20ml) and triethylamine (1 ml) at 5 °C. The reaction mixture was treated with 4-cyanobenzenesulphonyl chloride (0.40g). The reaction mixture was then stirred under argon for 4 hours allowing to warm to room temperature. The dichloromethane solvent was removed by evaporation and the residual pyridine solution poured into aqueous sodium hydrogen carbonate solution and then extracted with ethyl acetate. The organic extracts were then washed with aqueous sodium hydrogen carbonate solution, water, brine, dried ($MgSO_4$) and evaporated to yield a pale cream solid which was then recrystallised from ethyl acetate/isohexane to give 1-(4-pyridyl)-4-(4-cyanophenylsulphonyl)piperazine (0.31g) as a solid, m.p. 212-213 °C; microanalysis, found: C, 58.8; H, 4.9; N, 17.1%; $C_{16}H_{16}N_4O_2S$ requires: C, 58.5; H, 4.91; N, 17.1%; NMR: ($CDCl_3$) 3.18(t, 4H), 3.44(t, 4H), 6.62(dd, 2H), 7.88(q, 4H), 8.30(dd, 2H); MS: m/z 329 (MH)⁺.

Example 27

1-(4-Pyridyl)-4-(4-aminophenyl)piperazine (0.4g) was dissolved in dry dichloromethane (40ml) and cooled to 0° C. Triethylamine (0.4ml) was added followed by 4-cyanobenzenesulphonyl chloride (0.6g). The reaction mixture was then stirred overnight. The mixture was washed with aqueous sodium hydrogen carbonate solution, water, brine, dried (MgSO₄) and evaporated to yield the crude solid product. This solid was purified by flash chromatography on ICN Alumina (N 32-63) using and increasing concentrations of ethyl acetate in isohexane (50 - 100% ethyl acetate) and up to 10% methanol in ethyl acetate as the eluent to give 1-(4-pyridyl)-4-(4-cyanophenylsulphonamidophenyl)piperazine (0.12g) as a solid, m.p. 237-238° C; microanalysis found: C,61.4; H,4.9; N,15.5%; C₂₂H₂₁N₅O₂S.0.5 H₂O requires: C,61.7; H,4.9; N,16.3%; NMR: 3.17(t,4H), 3.42(t,4H), 6.81-6.97(m,6H), 7.82(d,2H), 8.02(d,2H), 8.18(d,2H); MS: m/z 420 (MH)⁺.

The 1-(4-pyridyl)-4-(4-aminophenyl)piperazine used as starting material was prepared as follows:

Sodium hydride (0.5g) (45-55% dispersion in oil) was added to a solution of 1-(4-pyridyl)piperazine (0.9g) in dry dimethylformamide (10ml) at ambient temperature and stirred for 30 minutes. After this time, 4-fluoronitrobenzene (0.65ml) was added slowly and the temperature raised to 70° C. The mixture was maintained at this temperature for 2 hours. The reaction mixture was then quenched by pouring into water and acidifying with aq 2N HCl solution to pH 1. The acidic layer was washed with diethyl ether and then basified with aq 2N NaOH solution. The resulting precipitate was filtered, washed with water, dissolved in methanol, filtered through phase separator paper and evaporated to dryness. The resulting crude material was recrystallised from methanol/ether to give 1-(4-pyridyl)-4-(4-nitrophenyl)piperazine (0.64g) as an oil. NMR: (CDCl₃) 3.61(q,8H), 6.58(d,2H), 6.81(d,2H), 8.16(d,2H), 8.33(bs,2H); MS: m/z 285 (MH)⁺.

A solution of sodium dithionite (2.5g) in water (10ml) was added to a warmed solution of 1-(4-pyridyl)-4-(4-nitrophenyl)piperazine (0.551g) in methanol (50ml) and the mixture was allowed to reflux for 2 hours. The methanol was removed by evaporation and the resulting concentrated solution was basified with solid Na₂SO₄. The organic material was extracted into ethyl acetate, washed with water, brine, dried (Na₂SO₄) and evaporated to give 1-(4-pyridyl)-4-(4-aminophenyl)piperazine (0.4g) as an oil. NMR: (CDCl₃) 3.14(t,4H), 3.48(t,4H), 6.68(m,4H), 6.85(d,2H), 8.31(bd,2H); MS: m/z 255 (MH)⁺.

Example 28

A solution of 4-chloropyrimidine HCl (450mg) and 4-bromophenyl sulphonyl piperazine (300mg) in ethanol (20ml) and water (2ml) containing triethylamine (0.5ml) was heated under reflux overnight. The solution was evaporated and water (50ml) added and the solution basified to pH 8 by addition of solid potassium carbonate to give a precipitate which was filtered and washed with water and air dried. The crude solid was dissolved in acetonitrile and chromatographed on an alumina column (ICN Alumina N 32-63) eluting with 30% tetrahydrofuran/ethyl acetate and then acetonitrile to give pure product which was recrystallised from a mixture of ethyl acetate/isohexane to give 1-(4-pyrimidyl)-4-(4-bromophenylsulphonyl)piperazine (44mg) as a solid, m.p. 196-197°C; microanalysis found: C, 43.9; H, 3.9; N, 14.4%; $C_{14}H_{13}BrN_4O_2S$ requires: C, 43.9; H, 3.9; N, 14.6%; NMR: 2.9-3.1(m, 4H), 3.6-3.8(m, 4H), 6.8(dd, 1H), 7.6-7.7(d, 2H), 7.8-7.9(d, 2H), 8.1-8.2(d, 1H), 8.5(s, 1H); MS: m/z 383 (MH)⁺.

The 1-(4-bromophenylsulphonyl)piperazine used as starting material was prepared as follows:

To a stirred solution of piperazine (10.8g) in dry dichloromethane (160ml) and triethylamine (20ml) at 0°C was added slowly a solution of 4-bromobenzenesulphonyl chloride (16g) in dichloromethane (80ml) and stirred for 24 hours. The reaction was then quenched by removal of the dichloromethane solvent by evaporation, taken up in water and extracted with ethyl acetate. The organic extracts were washed with aqueous sodium hydrogen carbonate solution, water, brine, dried (MgSO₄) and then evaporated to give a white crystalline solid which was recrystallised from ethyl acetate/isohexane to afford 1-(4-bromophenylsulphonyl)piperazine (14.1g) as a solid, m.p. 102-104°C; microanalysis found: C, 39.5; H, 4.4; N, 9.1%; $C_{10}H_{13}BrN_2O_2S$ requires: C, 39.4; H, 4.3; N, 9.2%; NMR (CDCl₃): 1.52(s, 1H), 2.97(dt, 8H), 7.61(d, 2H), 7.69(d, 2H); MS m/z 305 (MH)⁺.

Example 29

Carbonyl diimidazole (324mg) was added to a solution of 6-bromonaphthalene-2-sulphinic acid (658mg) in dimethylformamide (10ml). After stirring at ambient temperature for one hour N-4-(4-pyridyl)piperazine (326mg) was added as a solid in one portion and stirring continued at ambient temperature overnight. The reaction mixture was poured into ethyl acetate (100ml), washed with water (3 x 25ml), brine (25ml), dried (MgSO₄) and

evaporated to give a yellow oil which was purified by chromatography on silica gel (Mega Bond Elut column) using an increasing concentration of methanol in dichloromethane (up to 5% methanol) as eluant to give an oil which on trituration with diethyl ether gave a white solid 1-(4-pyridyl)-4-(6-bromonaphthalene-2-sulphenyl)piperazine (170mg), m.p. 200-202°C; microanalysis. found: C, 54.9; H, 4.4; N, 10.1; $C_{19}H_{18}BrN_3OS$ requires: C, 54.9; H, 4.3; N, 10.1; NMR: 2.9-3.0(m,2H); 3.1-3.3(m,2H); 3.35-3.5(m,4H); 6.8(dd,2H); 7.7-7.8(m,2H); 8.1-8.2(m,4H); 8.3(s,1H); 8.35(d,1H); MS: m/z 416 (MH)⁺.

Example 30

10 Triethylamine (3.48ml) was added to a stirred suspension of 1-(4-pyridyl)piperazine (4.08g) in DMF (50ml). The mixture was cooled to 4°C, and 4-nitrobenzoylchloride (4.64g) added. The mixture was stirred for 1 hour at 4°C and then for 16 hours at ambient temperature. Dichloromethane (250ml) was then added and the mixture washed with water (3 x 30ml), saturated brine (1 x 30ml), then dried (MgSO₄) and the solvents evaporated. The
15 residual oil was purified by flash chromatography on silica gel using 5% v/v methanol/dichloromethane and then with 10% v/v methanol/dichloromethane as eluant to give 1-(4-pyridyl)-4-(4-nitrobenzoyl)piperazine (5.09g) as a yellow solid. m.p. 158-160°C; microanalysis. found: C, 61.3; H, 5.3; N, 17.6%; $C_{16}H_{16}N_4O_3$ requires: C, 61.5; H, 5.2; N, 17.9%; NMR: 3.42(6H + H₂O, m), 3.87(2H, bs), 6.93(2H, d), 7.84(2H, d), 8.30(2H, d),
20 8.41(2H, d); MS: m/z 313 (MH)⁺.

Example 31

Azodicarbonyldipiperidine (20.03g), tributylphosphine (16.06g) and 1-(4-pyridyl)-4-piperidin-4-ol (9.43g) were added to a stirred solution of N-t-butyloxycarbonyl-4-
25 aminophenol (11.08g) in dry THF (300ml), cooled under a blanket of nitrogen to 10°C. A thick precipitate formed and the mixture was stirred at ambient temperature for 20 hours during which time the mixture slowly thinned. The precipitated tributylphosphine oxide was removed by filtration and the residue concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using ethyl acetate followed by dichloromethane
30 containing an increasing amount of methanol (up to 5% methanol) as eluent to give a solid (7.38g), mp 192-195°C.

A solution of this solid (4.22g) in dichloromethane (400ml) was treated with a saturated solution of hydrogen chloride in ether (50ml) and the mixture was stirred for 64 hours. The mixture concentrated *in vacuo* and the residue crystallised from methanol/ether to give 1-(4-pyridyl)-4-(4-aminophenyloxy)piperidine hydrochloride (2.85g), mp. 289-291°C. 5 NMR: 1.73 (m,2H), 2.06 (m,2H), 3.64 (m,2H), 3.94(m,2H), 4.76 (m,1H), 7.12(d,2H), 7.24(d,2H), 7.34(d,2H), 8.23(d,2H), 10.32 (broad, 2H); MS: m/z 270 (MH)⁺. This solid (1.5g) was dissolved in water (10ml) and 2M sodium hydroxide added until precipitation was complete. There was thus obtained 1-(4-pyridyl)-4-(4-aminophenoxy) piperidine free base as a brown solid (1.03g) mp 214-215°C: NMR: 1.57 (m,2H), 1.86 (m,2H), 3.24 (m,2H), 10 3.67(m,2H), 4.31 (m,1H), 6.47(d,2H), 6.66(d,2H), 6.87(d,2H), 8.13(d,2H); MS: m/z 270 (MH)⁺.

Example 32

A solution of N-(4-pyridyl)piperazine (815mg), 4-fluorobenzophenone (1.2 g) and 15 powdered potassium carbonate (912 mg) was stirred at 95°C in DMSO (10 ml) overnight. The solution was poured into water (150 ml) and extracted with dichloromethane (3x50 ml). The dichloromethane extracts were combined, washed with water, dried (Na₂SO₄) and evaporated. The residue was purified by chromatography on alumina (ICN Alumina N 32-63) using 1% methanol in dichloromethane as eluant to give a solid. The solid was recrystallised 20 from a mixture of ethyl acetate/isohexane to give 1-(4-benzoylphenyl)-4-(4-pyridyl)piperazine (450 mg) as a solid, m.p. 136-137°C.

Example 33

A solution of N-(4-pyridyl)piperazine (8.15 g), 4,4'-difluorobenzophenone (13.1 g) 25 and powdered potassium carbonate (9.12 g) was stirred at 95°C in DMSO (100 ml) overnight. The solution was poured into water (1500 ml) to give a precipitate which was filtered, washed with water and dried. The solid (7.82 g) was stirred in trifluoroacetic acid (25 ml) under argon with triethylsilane (10 ml) for 18 hours. The solution was poured into water (315 ml), taken to pH 12 with sodium hydroxide solution and extracted with dichloromethane (2x300 30 ml). The combined dichloromethane extracts were washed with water, dried (Na₂SO₄) and evaporated to give a residue which was purified by chromatography on alumina (ICN

Alumina N 32-63) using 0.5% methanol in dichloromethane as eluant. The solid obtained was recrystallised from a mixture of ethyl acetate/isohexane to give 1-(4-fluorobenzylphenyl)-4-(4-pyridyl)piperazine (350 mg) as a solid. m.p. 110-111°C.

5 Example 34

A solution of 1-(4-hydroxyphenyl)-4-(4-pyridyl)piperazine (670 mg), 4-fluorobenzonitrile (354 mg) and powdered potassium carbonate (445 mg) was stirred at 95°C in DMSO (12 ml) for 18 hours. The solution was poured into water (180 ml) to give a precipitate which was filtered, washed with water and dried. The solid was purified by chromatography on alumina (ICN Alumina N 32-63) using 1% methanol in dichloromethane as eluant. This gave a solid which was recrystallised from a mixture of ethyl acetate/isohexane to give 1-(4-cyanophenoxyphenyl)-4-(4-pyridyl)piperazine (126 mg) as a solid. m.p. 180-182°C.

The 1-(4-hydroxyphenyl)-4-(4-pyridyl)piperazine used as starting material was prepared as follows:

A solution of 4-chloropyridine HCl (450mg) and 1-(4-methoxyphenyl)-piperazine (226 mg) in ethanol (20 ml) and water (2 ml) containing triethylamine (0.5 ml) was heated under reflux for 18 hours. The solution was evaporated, water (50 ml) added and the solution taken to pH 8 by addition of solid potassium carbonate to give a precipitate which was filtered, washed with water and dried. The solid (33mg) was stirred in concentrated aqueous hydrogen bromide (2 ml) at 140°C for 8 hours, poured into cold water (2 ml) and taken to pH 7 with aqueous ammonia (1.3 ml) to give a solid which was filtered, washed with water and dried to give 1-(4-hydroxyphenyl)-4-(4-pyridyl)piperazine (28 mg). m.p. 288-290°C.

25 Example 35

Using an analogous procedure to that described in Example 34, but using 2-bromo-5-nitropyridine as starting material in place of 4-fluorobenzonitrile, there was prepared 1-(4-[5-nitro-2-pyridyloxy]phenyl)-4-(4-pyridyl)piperazine (50% yield). m.p. 174-175°C.

30 Example 36

Sodium hydride (120 mg) (50% dispersion in oil) was added to a stirred solution of 1-(4-hydroxyphenyl)-4-(4-pyridyl)piperazine (510 mg) in dimethylformamide (5 ml) under

argon. The solution was stirred at ambient temperature for 30 minutes and a solution of 4-cyanobenzylbromide (430 mg) in dimethyl formamide (5 ml) was added dropwise. The solution was stirred at ambient temperature overnight, water (150 ml) added to give a precipitate which was washed with water, dried and recrystallised from ethanol to give 1-(4-cyanobenzyloxyphenyl)-4-(4-pyridyl)piperazine (660mg), m.p. 212-214°C.

Example 37

Using an analogous procedure to that described in Example 36, but using 4-bromobenzylbromide as starting material in place of 4-cyanobenzylbromide, was prepared 1-(4-bromobenzyloxyphenyl)-4-(4-pyridyl)piperazine (50% yield), m.p. 233-235°C.

Example 38

A solution of 1-(4-formylphenyl)-4-(4-pyridyl)piperazine (1.0 g), 4-bromoacetophenone (745 mg) and conc. sodium hydroxide (3 drops) in ethanol (25 ml) was stirred at ambient temperature overnight to give a solid which was filtered, washed with ethanol and dried to give 1-(4-[4-bromobenzoyl ethyl]phenyl)-4-(4-pyridyl)piperazine (900mg), m.p. 201-203°C.

The 1-(4-formylphenyl)-4-(4-pyridyl)piperazine used as starting material was prepared as in Example 32, using 4-fluorobenzaldehyde as starting material in place of 4-fluorobenzophenone to give 1-(4-formylphenyl)-4-(4-pyridyl)piperazine (43% yield), m.p. 116-118°C.

Example 39

A solution of 1-(4-formylphenyl)-4-(4-pyridyl)piperazine (1.0 g), 4-methoxyacetophenone (503 mg) and concentrated sodium hydroxide (3 drops) in ethanol (25 ml) was stirred at ambient temperature overnight to give a solid which was dissolved in ethanol (100 ml) and hydrogenated over 10% palladium on charcoal to give a solid which was recrystallised from a mixture of ethyl acetate/isohexane to give 1-(4-[4-methylbenzoyl ethyl]phenyl)-4-(4-pyridyl)piperazine (400 mg), m.p. 114-115°C.

Example 40

4-Methoxybenzyltriphenylphosphonium bromide (4.47 g) was added to a solution of potassium t-butoxide (1.12 g) in tetrahydrofuran (50 ml) under argon. After 30 minutes at ambient temperature, the solution was treated with a solution of 1-(4-formylphenyl)-4-(4-pyridyl) piperazine (1.34 g) in tetrahydrofuran (25 ml) and the mixture stirred at ambient temperature overnight. The tetrahydrofuran was evaporated, the residue treated with water (100 ml) and extracted with dichloromethane (3x50 ml). The combined dichloromethane extracts were washed with water, dried (Na_2SO_4) and evaporated to give a residue which was purified by chromatography on alumina (ICN Alumina N 32-63) using 2% methanol in dichloromethane as eluant. This gave a solid which was recrystallised from a mixture of ethyl acetate/isohexane to give 1-[4-(4-methylphenylethynyl)phenyl]-4-(4-pyridyl)piperazine (350 mg) as a solid, m.p. 92-94°C.

Example 41

Using an analogous procedure to that described in Example 40, but using 4-cyanobenzyltriphenylphosphonium chloride as starting material in place of 4-methoxybenzyltriphenylphosphonium bromide, there was prepared 1-[4-(4-cyanophenylethynyl)phenyl]-4-(4-pyridyl)piperazine (18% yield), m.p. 105-106°C.

Example 42

A solution of 1-(4-acetylphenyl)-4-(4-pyridyl)piperazine (1.0g), benzaldehyde (177mg) and concentrated sodium hydroxide (3 drops) in ethanol (25 ml) was stirred at ambient temperature overnight to give a solid which was filtered, washed with ethanol and dried to give 1-(4-cinnamoylphenyl)-4-(4-pyridyl)piperazine (310mg), m.p. 208-210°C.

The 1-(4-acetylphenyl)-4-(4-pyridyl)piperazine used as starting material was prepared as in Example 32, using 4-fluoroacetophenone as starting material in place of 4-fluorobenzophenone to give 1-(4-acetylphenyl)-4-(4-pyridyl)piperazine (40% yield), m.p. 176-177°C.

Example 43

Using an analogous procedure to that described in Example 42, but using 4-tert-butylbenzaldehyde as starting material in place of benzaldehyde, there was prepared 1-[4-(4-tert-butylcinnamoyl)phenyl]-4-(4-pyridyl)piperazine (46% yield), m.p. 213-214°C.

Example 44

Using an analogous procedure to that described in Example 39, but using as starting material 1-(4-acetylphenyl)-4-(4-pyridyl)piperazine in place of 1-(4-formylphenyl)-4-(4-pyridyl)piperazine and 4-tolualdehyde in place of 4-methylacetophenone, was prepared 1-[4-(4-methylphenylpropionyl)-phenyl]-4-(4-pyridyl)piperazine (27% yield), m.p. 130-132°C.

Example 45

A solution of 4-(4-pyridyl)piperazine (5.0 g), bis(4-fluorophenyl)sulphone (15.58 g) and powdered potassium carbonate (6.35 g) was stirred at 95°C in DMF (30 ml) overnight. The solution was poured into water (150 ml) to give a black solid from which the aqueous phase was decanted. The solid was heated in ethanol and a brown solid was collected by filtration. The filtrate was evaporated and the residue was purified by chromatography on alumina (ICN Alumina N 32-63) first using ethyl acetate as eluent followed by 10 % methanol in dichloromethane. This gave 1-(4-fluorophenylphenylsulphone)-4-(4-pyridyl)piperazine as a yellow solid (521 mg); microanalysis: Found C, 63.3; H, 5.1; N, 10.9%; $C_{21}H_{20}FN_3O_2S$ requires: C, 63.5; H, 5.07; N, 10.6%.

Example 46

A mixture of 4-[3-(4-cyanophenoxy)-1-pyrrolidinyl]pyridine (269 mg) and powdered potassium hydroxide (568 mg) in t-butanol (10 ml), under an atmosphere of argon, was heated under reflux for 18 hours. The mixture was filtered hot. The filtercake was washed with water and ethanol to give 4-[3-(4-carbamoylphenoxy)-1-pyrrolidinyl]pyridine (166 mg) as a colourless solid, mp 298-300°C.

The 4-[3-(4-cyanophenoxy)-1-pyrrolidinyl]pyridine used as starting material was prepared as follows:

A solution of 4-chloropyridine hydrochloride (8.86 g), 3-pyrrolidinol (5.14 g) and triethylamine (14.8 ml) in water (65 ml) was stirred and heated under reflux for 65 hours. The solution was evaporated to a semi-solid. This residue was purified by flash column chromatography on silica (Merck 9385) using a 90:10:3 (v/v/v) mixture of ethyl acetate, methanol and aqueous ammonia solution as eluent, to give, after trituration with ethyl acetate,

- 4-(3-hydroxy-1-pyrrolidino)pyridine (5.95 g) as a cream solid, mp 207-209°C.

A solution of diethyl azodicarboxylate (1.73 ml) in dried tetrahydrofuran (10 ml) was added dropwise to a stirred mixture of triphenylphosphine (3.15 g), 4-cyanophenol (1.31 g) and 4-(3-hydroxy-1-pyrrolidinyl)pyridine (1.64 g) in dried tetrahydrofuran (45 ml), under an atmosphere of argon, at 5-7°C. The resulting solution was stirred at ambient temperature for 16 hours. The solid, which had separated, was filtered off and washed with diethyl ether to give 4-[3-(4-cyanophenoxy)-1-pyrrolidinyl]pyridine (823 mg) as an off-white solid, mp 182-185°C.

10 Example 47

A 2M solution of sodium methoxide in methanol (0.89 ml) was added to a suspension of ethyl 4-[4-(4-pyridyl)-1-piperazinyl]benzoate (500 mg) in a 33% solution of monomethylamine in ethanol (15 ml). The mixture was stirred at 40°C for 18 hours. The mixture was cooled and the solid was collected by filtration. The solid was washed with ethanol and ether to give 1-(4-methylcarbamoylphenyl)-4-(4-pyridyl) piperazine (374 mg) as a cream solid, mp 239-242°C.

The ethyl 4-[4-(4-pyridyl)-1-piperazinyl]benzoate used as starting material was prepared as follows:

A solution of 4-(4-pyridyl)piperazine (9.78 g), ethyl 4-fluorobenzoate (9.7 ml) and powdered potassium carbonate (9.9 g) in dried dimethylsulphoxide (60 ml) was heated at 95°C for 18 hours. The mixture was poured into water (1200 ml) and stirred for 30 minutes. The precipitate was filtered off, washed with water and dried. The solid was purified by flash column chromatography on alumina (ICN alumina N32-63) using 1% methanol / dichloromethane as eluent, to give ethyl 4-[4-(4-pyridyl)-1-piperazinyl]benzoate (4.85 g) as a cream solid, mp 162-164°C.

Example 48

Oxalyl chloride (0.25 ml) was added dropwise to a stirred suspension of 4-[1-(4-pyridyl)piperazin-4-yl]benzoic acid (530 mg) in dried dichloromethane (20 ml) containing dimethylformamide (1 drop). The mixture was stirred at ambient temperature for 1.5 hours and evaporated to dryness. The residue was suspended in dried dichloromethane (25 ml).

t-Butylamine (2 ml) was added slowly to this stirred suspension at 5°C. The mixture was stirred at ambient temperature for 3 hours, then evaporated to dryness. The residue was suspended in aqueous sodium hydrogen carbonate solution (30 ml) and the mixture was extracted with ethyl acetate (3 x 60 ml). The ethyl acetate extracts were combined, washed successively with aq NaHCO₃ solution (30 ml) and saturated brine (30 ml), dried (Na₂SO₄) and evaporated to dryness. The residue was recrystallised from ethyl acetate (25 ml) to give 1-(4-t-butylcarbamoylphenyl)-4-(4-pyridyl)piperazine (390 mg) as a colourless solid mp 214-217°C.

The 4-[1-(4-pyridyl)piperazin-4-yl]benzoic acid used as starting material was prepared as follows:

1M sodium hydroxide solution (103 ml) was added to a suspension of ethyl 4-[4-(4-pyridyl)-1-piperazinyl]benzoate (10.3 g) in ethanol (200 ml) and the mixture was stirred at ambient temperature for 16 hours. The solution was evaporated to dryness. The residue was stirred in water (515 ml) for 15 minutes and any insoluble material was filtered off. The filtrate was treated with ice-cooled 1M hydrochloric acid (103 ml). The precipitate was filtered off, slurry washed with water, sucked dry and dried over phosphorus pentoxide, at 50°C for 2 days to give 4-[1-(4-pyridyl)piperazin-4-yl]-benzoic acid (5.24 g) as an off-white solid, mp >300°C.

20 Example 49

Using an analogous procedure to that described in Example 48, but using n-butylamine as starting material in place of t-butylamine, was prepared 1-(4-n-butylcarbamoylphenyl)-4-(4-pyridyl)piperazine (67% yield) as a colourless solid, mp 172-174°C.

25

Example 50

1-(4-Methoxycarbonylphenylmethyl)-4-(4-pyridyl)piperazine (933mg; 3.0mmol) was dissolved in methanol (8ml) and treated at ambient temperature under an argon atmosphere with an excess of piperidine (~20 equivalents) and 2M sodium methoxide in methanol (3ml). The resulting solid suspension was heated at 65°C under reflux for 20 hours and then allowed to cool to room temperature. The reaction mixture was treated with a saturated aqueous solution of sodium hydrogen carbonate and extracted with CH₂Cl₂. The organic extracts were

washed with water and brine, dried over MgSO_4 , filtered and evaporated to yield an impure solid. The solid was chromatographed on silica gel (Varian bond elut-trademark) prepacked silica column, eluting with a mixture of methanol (1%), ammonium hydroxide (1%) and dichloromethane (98%) to give 1-(4-N-piperidinocarbonylphenylmethyl)-4-(4-pyridyl)piperazine (386% yield), NMR (CDCl_3): 1.51-1.73 (m, 6H), 2.58 (t, 4H), 3.28 (t, 4H), 3.49 (s, 4H), 3.57 (s, 2H), 6.64 (dd, 2H), 7.30 (s, 4H), 8.25 (dd, 2H).

The 1-(4-methoxycarbonylphenylmethyl)-4-(4-pyridyl)piperazine used as starting material was prepared as follows :

4-Pyridyl piperazine (3.26g) was dissolved in 20ml of 10% water in iso-propanol and treated at ambient temperature, with agitation, with methyl 4-bromomethyl benzoate (4.58g) and triethylamine (10ml). The resulting yellow suspension was stirred vigorously for 30 minutes at room temperature and then heated at 100°C under reflux for 20 hours. The suspension cleared to become a yellow solution when the reaction temperature had reached 60°C . After this period of heating the reaction mixture was allowed to cool to room temperature and the solvent removed by rotary evaporation under reduced pressure to yield an amber slurry. The slurry was treated with 2N aqueous sodium hydroxide and extracted with dichloromethane. The organic extracts were washed with saturated brine, dried over MgSO_4 , filtered and evaporated down to an amber oil, which, after drying over 60 hours on a high vacuum pump yielded a pale yellow solid, 4.63g (74%).

Example 51

Using a similar method as described in Example 50 but using methylamine in place of piperidine there was obtained 1-(4-N-methylaminocarbonylphenylmethyl)-4-(4-pyridyl)piperazine (76% yield), m.p. $188-190^\circ\text{C}$.

Example 52

1-(4-Carboxyphenylmethyl)-4-(4-pyridyl)piperazine (594mg) was suspended in dichloromethane (25ml) and treated at ambient temperature with thionyl chloride (5ml) and heated at 40°C over 18 hours. After this period the reaction mixture was allowed to cool to room temperature, evaporated to dryness, azeotroped with toluene and dried under high vacuum for 2 hours. The yellow solid obtained was suspended in dichloromethane (20ml), stirred in an ice bath and treated at $0-5^\circ\text{C}$ with 5 equivalents of morpholine. The suspension

was allowed to warm to ambient temperature and stirred for 18 hours. After this period the reaction mixture was treated with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic extracts were then washed with water and saturated brine, dried over MgSO_4 , filtered and evaporated down to yield an impure solid. The solid was
5 purified by chromatography on silica gel (Varian bond elut-trademark) prepacked silica column with a mixture of methanol (1-4%), ammonium hydroxide (1%) in dichloromethane to give 1-(4-N-morpholinocarbonylphenylmethyl)-4-(4-pyridyl)piperazine (33% yield) m.p. 121-125°C.

The 1-(4-carboxyphenylmethyl)-4-(4-pyridyl)piperazine used as starting material was
10 prepared as follows :

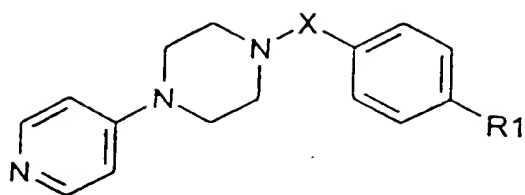
1-(4-Methoxycarbonylphenylmethyl)-4-(4-pyridyl)piperazine (4.5g) was dissolved in methanol (50ml) and treated at ambient temperature with 2M aqueous sodium hydroxide (36ml). The resulting solution was stirred at room temperature for 3 hours and concentrated by evaporation to an aqueous solution of the sodium salt of the acid. This solution was just
15 acidified with glacial acetic acid (4.3ml) to give a white precipitate which was collected by filtration, washed with water and dried to give 1-(4-carboxyphenylmethyl)-4-(4-pyridyl)piperazine in 90% yield.

Example 53

20 Using a similar method to that described in Example 52 but using ethylamine in place of morpholine there was obtained 1-(4-ethylaminocarbonylphenylmethyl)-4-(4-pyridyl)piperazine (51% yield), m.p. 213-215°C.

Example 54

25 Using a similar method to that described in Example 50 there was obtained the following compounds.



5

X	R ₁	mp (°C)
CH ₂		144-147
CH ₂		145-147

10 Example 55

Ethyl magnesium chloride (3M) in anhydrous THF (1.0ml) was treated at room temperature under argon with a solution of 1-(4-acetylphenyl)-4-(4-pyridyl)piperazine (281mg) in anhydrous THF (15ml). The resulting solid suspension was heated at 70°C under reflux for 3 hours. The mixture was cooled in ice at 0-5°C and treated with diethyl ether and a saturated solution of aqueous ammonium chloride. The reaction mixture was stirred for 10 minutes with ice cooling and at room temperature for 10 minutes. The aqueous phase was then extracted with dichloromethane and the ether phase was evaporated. The residue was dissolved in dichloromethane and combined with the other organic extracts. The combined extracts were then washed with saturated brine, dried over MgSO₄, filtered and evaporated to give an impure orange solid. The solid was purified by chromatography on a prepacked silica

column (Varian bond elut-trademark), eluting with a mixture of methanol (1-2%) and ammonium hydroxide (1%) in dichloromethane to obtain a pale yellow solid which was triturated with diethyl ether to give 1-(4-(1-hydroxy-1-methylethyl)phenyl)-4-(4-pyridyl)piperazine (21% yield) as a pale yellow solid, m.p. 234-235°C.

5

Example 56

4-(5-Cyano-2-pyridinoxy)piperidine (337 mg) and 4-chloropyridine hydrochloride (284 mg) were dissolved in water (10 mL) and treated with triethylamine (0.47 mL) in isopropanol (1 mL) and refluxed for 24 hours. The reaction was quenched by evaporation of the solvent. The residue was dissolved in dichloromethane and washed with aqueous sodium hydrogen carbonate solution, water, brine, dried (MgSO_4) and evaporated. The residue was triturated with diethyl ether to give 1-(4-pyridyl),4-(5-cyano-2-pyridinyloxy)piperidine (50 mg) as a pale cream crystalline solid; microanalysis, found: C, 66.4; H, 5.6; N, 19.0%; $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O} \cdot 0.5\text{H}_2\text{O}$ requires: C, 66.4; H, 5.9; N, 19.4%; NMR: (CDCl_3) 1.90 (m, 2H), 2.10 (m, 2H), 3.32 (m, 2H), 3.67 (m, 2H), 5.37 (m, 1H), 6.68 (d, 2H), 6.80 (d, 1H), 7.78 (dd, 1H), 8.28 (d, 2H), 8.47 (d, 1H); MS: m/z 281 (MH^+).

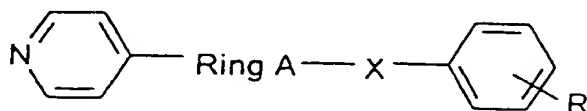
The 4-(5-cyano-2-pyridinoxy)piperidine starting material was prepared as follows:
To a solution of 1-(t-butyloxycarbonyl)-4-piperidinol (600 mg) in dry DMF (20 mL) was added sodium hydride (0.24g, 50% dispersion in oil) and stirred under argon for 1 hour. 2-Chloro-5-cyanopyridine (0.44 g) was added and the mixture was heated at 70°C overnight. The reaction was quenched by pouring into water and extracted with diethyl ether. The extract was washed with water, brine, dried (MgSO_4) and evaporated. The residue was then chromatographed on silica gel eluting with a mixture of dichloromethane (25%) in isohexane increasing to dichloromethane. The residue was recrystallised from isohexane to afford 1-(t-butyloxycarbonyl),4-(5-cyano-2-pyridinyloxy)piperidine (400 mg) as a colourless crystalline solid; NMR: (CDCl_3) 1.46 (s, 9H), 1.64 - 1.82 (m, 2H), 1.92 - 2.09 (m, 2H), 3.21 - 3.36 (m, 2H), 3.70 - 3.84 (m, 2H), 5.28 (m, 1H), 6.78 (d, 1H), 7.77 (dd, 1H); MS: m/z 304 (MH^+).

To 1-(t-butyloxycarbonyl),4-(5-cyano-2-pyridinyloxy)piperidine (1.6 g) in dichloromethane (20 mL) was added trifluoroacetic acid (1.2 mL) and the reaction stirred at room temperature for 1 hour. The reaction was quenched by evaporation of trifluoroacetic acid dissolving the residue in water, basifying with sodium hydrogen carbonate and extracting

with dichloromethane. The organic layer was then washed with water, brine, dried (MgSO_4) and evaporated to yield 4-(5-cyano,2-pyridyloxy)piperidine as a white crystalline solid (337 mg), MS: m/z 279 (MH^+).

5 Example 57

Using the procedure described in Example 1, the following compounds were prepared.



Compound No	Ring A	X	R	m.p. (°C)
1 ^a	1-piperazin-4-yl	-	4- CH_2NH_2	167-168
2	1-piperazin-4-yl	-	4-fluorophenyl-sulphonamidomethyl	169-170
3	1-piperazin-4-yl	-	3-nitrophenyl-sulphonamidomethyl	10.66 minutes *
4	1-piperazin-4-yl	-	3,4-dimethoxy-phenylsulphonamidomethyl	11.43 minutes *
5	1-piperazin-4-yl	-	2,4,5-trichloro-phenylsulphinamidomethyl	13.03 minutes *
6	1-piperazin-4-yl	-	2-chloro-4-cyanosulphonamido-methyl	10.64 minutes *
7	1-piperazin-4-yl	-	3,4-dimethyl-sulphonamidomethyl	12.53 minutes *
8	1-piperazin-4-yl	-	4- <i>t</i> -butyl-sulphonamido methyl	13.68 minutes *
9	1-piperazin-4-yl	-	2-nitro sulphonaminomethyl	10.56 minutes *
10 ^b	1-pyrrolidin-3-yl	0	4-cyano	174-175

[a] see intermediate in Example 1.

[b] prepared using the method of Example 31.

* retention time on HPLC column:

5

Column HYPERSIL ODS 5 μ

Flow Rate 1.5ml/min

Detector Wavelength 280 λ

Oven Temperature 40 °C

10 Solvent C 30 mmol Et₃N/H₂O

Solvent D 30 mmol Et₃N/CH₃CN

Time	% Solvent C	% Solvent D
0	95	5
3	95	5
17	5	95
18	95	5
20	95	5

Example 58

15 A solution of 4-pyridyl piperazine (9.78g), 4-fluorobenzonitrile(7.26g) and powdered

potassium carbonate(10g) was stirred and heated in DMSO(100ml) at 100°C for 18 hours.

The solution was poured into water (500ml) to give a precipitate which was filtered and

washed with water. The crude solid was dried in a vacuum oven for 18 hours. The residue

was dissolved in dichloromethane and purified by flash chromatography on alumina (ICN

20 Alumina N 32-63) using an increasing concentration of ethyl acetate in dichloromethane (up

to 100% ethyl acetate) as eluant to give a solid which was recrystallised from ethyl

acetate/isohexane to give 1-(4-cyanophenyl)-4-(4-pyridyl)piperazine (7.5g) as a solid.

m.p.157-158°C; microanalysis. found: C,72.7;H,6.1;N,21.0%;C₁₆H₁₆N₄ requires:

C,72.7;H,6.1;N,21.2%; NMR (dmso-d₆):3.45-3.55(8H,bs):6.8-6.9(2H,d):7.0-7.1(2H,d); 7.55-

25 7.65(2H,d):8.1-8.2(2H,d); MS m/Z 265 (M+H).

Example 59

A solution of 1-(4-cyanophenyl)-4-(4-pyridyl)piperazine (1.8g) in ethanol saturated with ammonia gas (150ml) was hydrogenated at 150 atmospheres and 100°C over Raney Nickel as catalyst for 18 hours. The solution was filtered through Celite and the filtrate evaporated to dryness. The residue was purified by flash chromatography on alumina (ICN Alumina N 32-63) using a mixture of 95:5 dichloromethane:methanol as eluant to give a solid which was recrystallised from tetrahydrofuran/isohexane to give 1-(4-(aminomethyl)phenyl)-4-(4-pyridyl)piperazine (1.3g) m.p. 168-170°C; microanalysis, found: 10 C, 71.5; H, 7.6; N, 20.5%; $C_{16}H_{20}N_4$ requires: C, 71.6; H, 7.5; N, 20.9%; NMR (dmso-d₆): 3.2-3.4(4H.m); 3.4-3.6(4H.m); 3.65(2H.s); 6.8-6.9(2H.d); 6.9-7.0(2H.d); 7.15-7.25(2H.d); 8.15-8.25(2H.d); MS: m/z 269 (M+H)

Example 60

15 To a solution of 6-chloronicotinic acid (188mg.) in tetrahydrofuran (5 ml), was added 1,1'-carbonyldiimidazole (178 mg) and the solution stirred for 1 hour. A solution of 1-(4-(2-aminoethyl)phenyl)-4-(4-pyridyl)piperazine (268 mg) in tetrahydrofuran (10 ml) was then added in one portion and the resulting solution stirred at ambient temperature overnight. The solution was evaporated to dryness and tetrahydrofuran (2ml) and aqueous sodium bicarbonate 20 (10 ml, 1 molar) were added to the residue which was stirred vigorously for thirty minutes. The solution was filtered and the residue washed with water and air dried to give 1-(4-pyridyl)-4-[4-(6-chloronicotinamidomethyl)phenyl]piperazine (230 mg) as a solid, m.p. 208-210°C; microanalysis found: C, 63.5; H, 5.3; N, 16.8; $C_{22}H_{22}ClN_5O \cdot 0.5H_2O$ requires: C, 63.5; H, 5.5; N, 16.8; NMR (dmso-d₆): 3.2-3.3(m, 4H), 3.4-3.5(m, 4H), 4.35-4.45(d, 2H), 6.8-25 6.85(d, 2H), 6.9-7.0(d, 2H), 7.15-7.25(d, 2H), 7.57-7.63(d, 2H), 8.1-8.2(d, 2H), 8.25-8.35(dd, 1H), 8.65-8.7(d, 2H), 9.07-9.17(bt, 1H); MS m/z 408 (M+H)

Example 61

A solution of 2,4-dichloropyrimidine (1.5g), sodium bicarbonate (1.0g) and 1,4-30 piperazinyl 4 benzonitrile (1.8g) in ethanol (50 ml) was stirred and heated under reflux for 18 hours. Water (200ml) was added to give a precipitate which was filtered washed with water

and recrystallised twice from a mixture of tetrahydrofuran and hexane to give 1-(4-cyanophenyl)-4-(2-chloropyrimidin-4-yl)piperazine (1.73g) m.p. 216-218 °C

Example 62

5 To a solution of benzoic acid (122mg) in dimethylformamide (2 ml), was added 1,1'-carbonyldiimidazole (188 mg) in dimethylformamide (2ml) and the solution stirred at ambient temperature for 1 hour. A solution of 1-[4-(2-aminoethyl)phenyl]-4-(4-pyridyl)piperazine (268 mg) in dimethylformamide (4 ml) was then added in one portion and the resulting solution stirred at ambient temperature for twelve hours. The solution was
10 evaporated to dryness and aqueous sodium bicarbonate (8 ml, 1M) added. The mixture was stirred vigorously at ambient temperature for thirty minutes. The solid was collected by filtration, washed with water to give 1-(4-pyridyl)-4-(benzoyl-aminomethyl-phenyl)piperazine (389mg), retention time 11.49mins (same HPLC conditions as in Example 57).

15

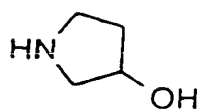
Example 63

In a similar manner to Example 62, 1-(4-pyridyl)-4-(4-(3-thienylcarbonylaminomethyl)phenyl) was prepared (386mg), retention time 14.59 minutes.

Piperazine

20 Examples 64-96

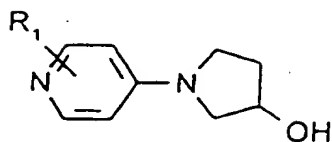
The following compounds are conveniently prepared according to the following general synthetic methods:



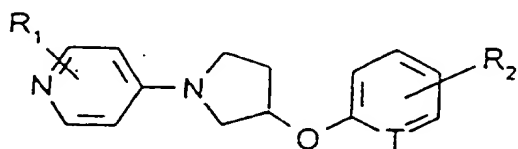
Method A

1. (BOC)₂, aq. NaOH
2. Methods B, D or E
3. Method C

5

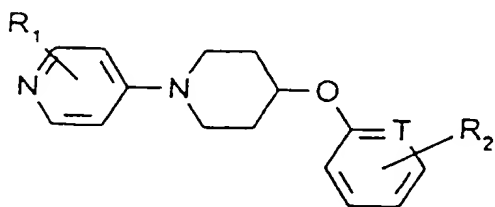


Methods B, D or E

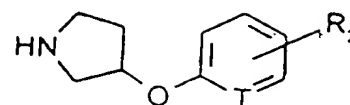


10

and analogous alternatives for:



(where T = N or CH)



Method A

15 In a typical procedure for Method A the neutral amine (or salt thereof) is mixed with a pyridine substituted in the 4-position with a suitable leaving group such as Cl, Br, or methanesulphonyloxy (or salt thereof) in the presence of a suitable base such as a tertiary amine, a metal alkoxide or a metal carbonate salt. The reaction is typically carried out at from room temperature to 150°C, preferably at about 100°C, in a suitable solvent such as water, an
20 alcohol or xylenes.

The starting amines are conveniently prepared by removal of a standard protecting group such as t-butyloxycarbonyl. The reaction is performed in the presence of a strong acid such as trifluoroacetic acid or a mineral acid, optionally in a solvent such as water or

W0 7/120120
dichloromethane, typically according to Method C. The reaction is typically carried out at from -20°C to 100°C, preferably at about room temperature.

In a typical procedure for Methods B and D the alcohol is mixed with a pyridine substituted in the 2-position with a suitable leaving group such as Cl, Br, or
5 methanesulphonyloxy (or salt thereof), or a benzene substituted with a similarly appropriate leaving group, in the presence of a suitable base such as a metal hydride, a metal alkoxide or a metal amide and optionally a phase transfer catalyst such as a tetralkylammonium salt. The reaction is typically carried out at from -20°C to 100°C, preferably at about room temperature, and may optionally be performed in the presence of a solvent such as tetrahydrofuran, toluene,
10 dichloromethane or N,N-dimethylformamide.

In a typical procedure for Method E the alcohol is mixed with a phenol or 2-pyridone derivative in the presence of a suitable azodicarboxylate derivative such as diisopropylazodicarboxylate and a phosphine derivative such as triphenylphosphine or tri-n-butylphosphine, or any other such variant on the general method originally defined by O.
15 Mitsunobu *et al.* (*Bull. Chem. Soc. Jpn.*, 1971, 44, 3427). The reaction is typically carried out at from -20°C to 100°C, preferably at about room temperature, in a solvent such as tetrahydrofuran, toluene or dichloromethane under an inert atmosphere such as nitrogen or argon.

Alternatively the alcohol may be derivatised as a sulphonyl ester (such as
20 methanesulphonyl) or halide, and the typical leaving group so generated may be displaced by a suitable salt of the phenol or 2-pyridone derivative (such as the lithium, sodium or potassium salt), optionally in the presence of a phase transfer catalyst such as a tetralkylammonium salt (as in Method G). The reaction is typically carried out at from -20°C to 100°C, preferably at about room temperature, and may optionally be performed in the
25 presence of a solvent such as tetrahydrofuran, toluene, dichloromethane or N,N-dimethylformamide.

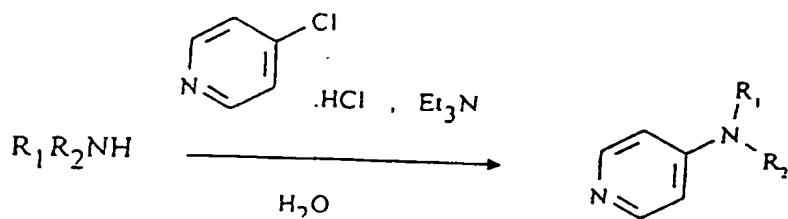
In a typical procedure for Method F the piperazine is mixed with a heterocycle substituted with a suitable leaving group such as Cl, Br, or methanesulphonyloxy (or salt thereof), or a benzene derivative substituted with a similarly appropriate leaving group. The
30 reaction is typically carried out at from 0°C to 150°C, preferably at about 70°C, in a solvent such as water, a suitable alcohol, toluene or other substituted benzene derivatives, under an inert atmosphere such as nitrogen or argon.

The starting materials for the above methods are either known compounds or may be prepared by conventional procedures in accordance with literature precedents.

General synthetic methods:

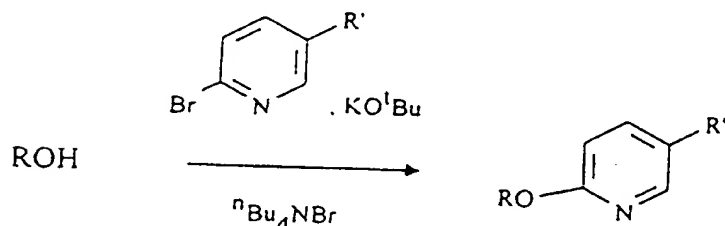
Method A:

5



The amine (1.0 equivalent) and 4-chloropyridine hydrochloride (1.0 equivalent) were dissolved in H₂O (0.88M in each reagent) and Et₃N (1.8 equivalent) was added at ambient temperature. The mixture was heated at reflux until reaction was complete.

Method B:

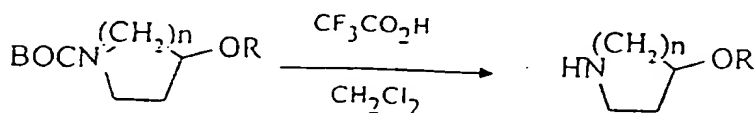


15

Under argon, potassium t-butoxide (2.0 equivalent) and alcohol (1.0 equivalent) were stirred together for 5 minutes. Tetra-n-butylammonium bromide (0.06 equivalent) was added followed by the 2-halopyridine (1.53 equivalent). If necessary, the mixture was heated at 80°C until reaction was complete.

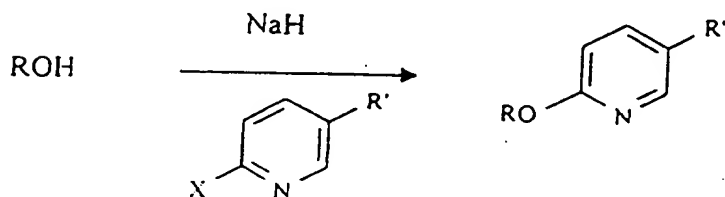
20

Method C:



The carbamate (1.0 equivalent) in CH_2Cl_2 (0.88M) was cooled to 5 °C and trifluoroacetic acid (0.33x volume of CH_2Cl_2) was added dropwise. The mixture was warmed to ambient temperature and stirred until reaction was complete.

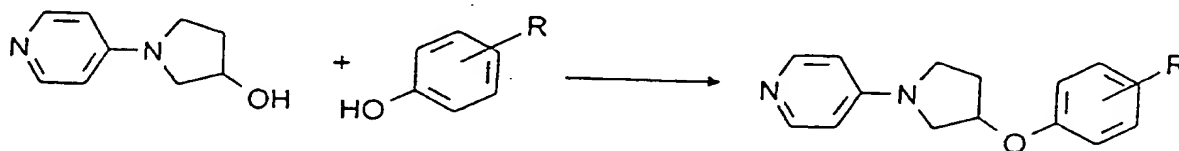
5 Method D:



Sodium hydride (60% dispersion in paraffin oil, 146mg, 1.2 equivalent) was added to an oven-dried round-bottomed flask and washed under an argon atmosphere with pentane. DMF (5ml) was then added, followed by the alcohol (1.0 equivalent, 3.05mmol) and tetra-n-butylammonium bromide (59mg, 0.18mmol). The mixture was added as a slurry to the 2-halo-pyridine (1.5 equivalent) in a second dry flask under argon, with stirring. After the reaction was complete the solvent was evaporated under vacuum.

15

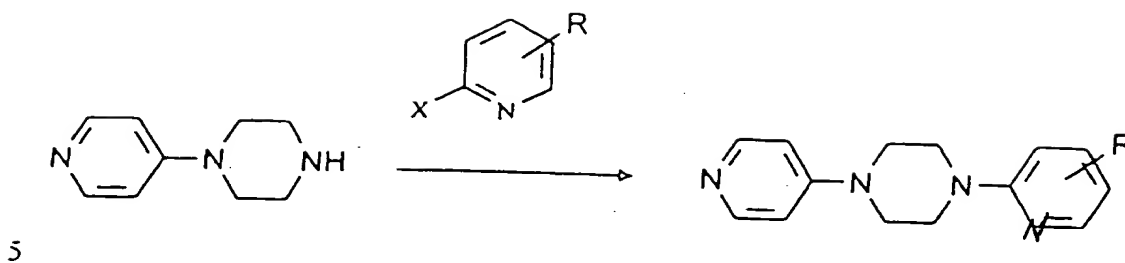
Method E:



Under argon, the alcohol (1 equivalent), phenol (1 equivalent) and triphenylphosphine (1.44 equivalents) were mixed together in THF (0.3M solution) and cooled in an ice-bath. Diisopropylazodicarboxylate (1.53 equivalents) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. All volatiles were removed under reduced pressure, and the residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 7% MeOH/ CH_2Cl_2 ; 7%MeOH/1% NH_4OH / CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 .

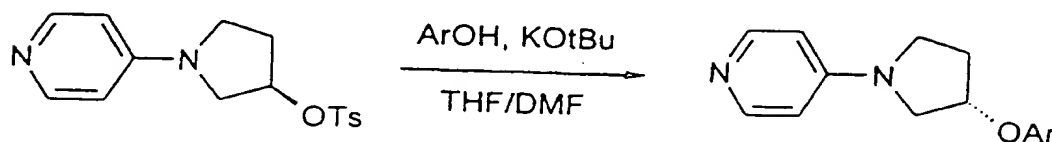
25

Method F:



1-(4-pyridyl)-piperazine (1.0 equivalent) was heated with the appropriate 2-halopyridine (1.0 equivalent) and triethylamine (1.0 equivalent) in aqueous t-butanol (1:10; 0.41M) at reflux until reaction was complete.

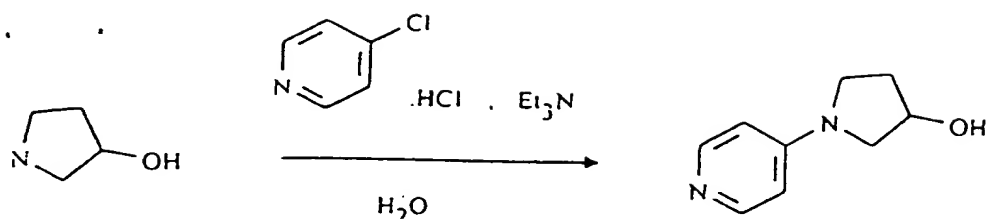
10 Method G:



15 The phenol (0.94mmol) was suspended in THF (1M) under argon. 1ml potassium t-butoxide solution (1M in THF) was then added, followed by the relevant tosylate (0.94mmol in 2ml DMF). The reaction was heated at reflux overnight, whereupon the solvents were removed under vacuum.

20 Intermediates

1-(4-Pyridyl)-3-hydroxypyrrolidine



Scale: 5g, 57.4mmol

5

Method A. Work-up: the reaction mixture was cooled in an ice bath for 1 hour. The resultant white solid was filtered off and washed with ice water (30 ml) and dried overnight *in vacuo* in the presence of silica gel. The product was given as fine white powder.

Yield 5.78g (61%).

10 $R_f = 0.1$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, DMSO-d₆): $\delta = 2.0$ (m, 2H), 3.22 (m, 1H), 3.7 (m, 3H), 4.4 (m, 1H), 5.0 (s, OH), 6.32 (m, 2H), 8.15 (m, 2H).

MS (ESP+): m/e 165 (M+H)⁺.

15 (R)-1-(4-Pyridyl)-3-hydroxypyrrolidine

Made by the method used for racemic material. The NMR spectrum, mass spectrum and R_f were as for the racemic material, and the R enantiomer gave an optical rotation (α_D) of -22.5 (c=10mg/ml, MeOH).

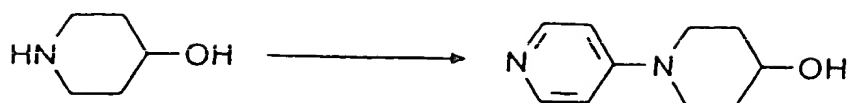
20

(S)-1-(4-Pyridyl)-3-hydroxypyrrolidine

Made by the method used for racemic material. The NMR spectrum, mass spectrum and R_f were as for the racemic material, and the S enantiomer gave an optical rotation (α_D) of +22.7

25 (c=10mg/ml, MeOH).

1-(4-Pyridyl)-4-hydroxypiperidine



Scale: 26.9g, 0.266mol

5

Method A, using 4-hydroxypiperidine. Work-up: pH adjusted to 14 with aq. NaOH. Solid product filtered. Taken up with H₂O & pH adjusted to 8.5. The solid product was filtered, dissolved in MeOH & preadsorbed onto silica. Column chromatography, eluting with 10%MeOH/CH₂Cl₂, increasing to 20%MeOH/5%PrNH₂/CH₂Cl₂ gave the product as a sticky solid.

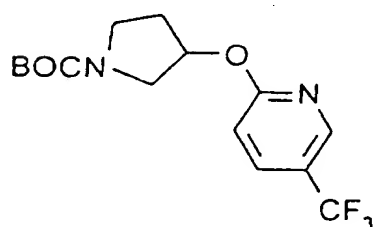
Yield 22.25g (47%).

R_f = 0.25 (20%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (DMSO-d₆): δ = 1.4 (m, 2H), 1.6 (m, 2H), 3.05 (m, 2H), 3.5 (m, 3H), 6.6 (m, 2H), 8.1 (m, 2H).

15 MS (ESP+): m/e 179.5 (M+H)⁺.

1-(t-butoxycarbonyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



20 Scale: 4.99g, 24.9mmol

Method B, using 1-(t-butoxycarbonyl)-3-hydroxypyrrolidine. The crude product was partially purified by column chromatography on silica, eluting with 10%MeOH/CH₂Cl₂. Further purification by column chromatography on silica, eluting with 10%Et₂O/CH₂Cl₂, gave the product as an oily solid.

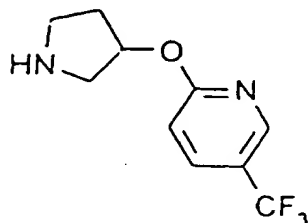
Yield 7.44g (83%).

R_f = 0.81 (10% Et₂O/CH₂Cl₂)

$^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 1.48 (s, 9H), 2.2 (m, 2H), 3.6 (m, 4H), 5.6 (m, 1H), 6.6 (d, 1H), 7.77 (dd, 1H), 8.42 (s, 1H).

MS (ESP+): m/e 333 ($\text{M}+\text{H}$) $^+$.

5 3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



Scale: 7.34g, 22mmol

10

Method C. The solvents were evaporated and the residue partitioned between Et_2O and aq. HCl. The aqueous layer was basified with K_2CO_3 and extracted with CH_2Cl_2 . The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give an orange gum.

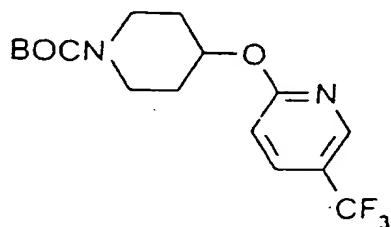
Yield = 3.3g (64%)

15 R_f = 0.83 (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 1.95 (m, 1H), 2.15 (m, 1H), 2.95 (m, 1H), 3.16 (m, 3H), 5.53 (m, 1H), 6.78 (d, 1H), 7.74 (dd, 1H), 8.42 (m, 1H).

MS (ESP+): m/e 233 ($\text{M}+\text{H}$) $^+$.

20 1-(t-butoxycarbonyl)-4-(5-trifluoromethyl-2-pyridyloxy)piperidine



Scale: 4.99g, 24.9mmol

Method B. The crude product was partially purified by column chromatography on silica, eluting with EtOAc/hexane (0% to 25% in increments of 5%).

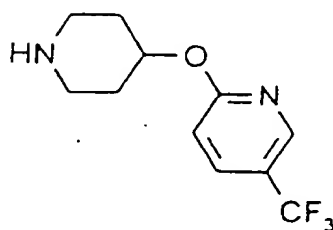
$R_f = 0.42$ (20%EtOAc/hexane)

¹H-NMR (200MHz, CDCl₃): $\delta = 1.48$ (s, 9H), 1.75 (m, 2H), 2.0 (m, 2H), 3.3 (m, 2H), 3.78 (m, 2H), 5.3 (m, 1H), 6.78 (d, 1H), 7.77 (dd, 1H), 8.4 (s, 1H).

MS (ESP+): m/e 347 (M+H)⁺.

4-(5-trifluoromethyl-2-pyridyloxy)piperidine

10



Scale: 9.2g (impure), ca. 25mmol

15 Method C. The solvents were evaporated and the residue partitioned between CH₂Cl₂ and aq. K₂CO₃. The organic phase was dried over anhydrous Na₂SO₄ and evaporated to give an orange gum. After trituration with Et₂O the product was isolated as an off-white solid.

Yield = 3.58g (55%)

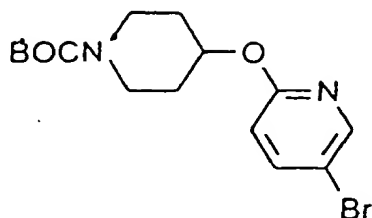
$R_f = 0.19$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

20 ¹H-NMR (250MHz, CDCl₃): $\delta = 1.7$ (m, 2H), 2.1 (m, 2H), 2.85 (m, 2H), 3.15 (m, 2H), 5.25 (m, 1H), 6.75 (d, 1H), 7.75 (dd, 1H), 8.4 (d, 1H).

MS (ESP+): m/e 247 (M+H)⁺.

1-(t-butoxycarbonyl)-4-(5-bromo-2-pyridyloxy)piperidine

25



Scale: 0.79g, 3.93mmol

Method: under argon, 1-(t-butyloxycarbonyl)-4-hydroxypiperidine (0.79 g, 3.93 mmol), 5-bromo-2-pyridone (0.49 g, 3.02 mmol) and triphenylphosphine (1.14 g, 4.35 mmol) were dissolved in THF (20 ml). To the mixture was added diisopropylazodicarboxylate (0.91 ml, 4.62 mmol) dropwise at ambient temperature followed by stirring for 18 hours. The mixture was concentrated *in vacuo* and applied to the top of a silica column. Elution with solvent of increasing concentration of EtOAc in CH₂Cl₂ and evaporation *in vacuo* of the relevant 10 fractions gave the product.

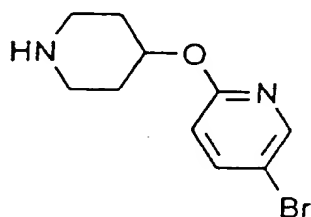
Yield = 640mg (61%)

R_f = 0.63 (EtOAc)

¹H-NMR (200MHz, CDCl₃): δ = 1.46 (s, 9H), 1.7 (m, 2H), 1.92 (m, 2H), 3.25 (m, 2H), 3.75 (m, 2H), 5.15 (m, 1H), 6.61 (d, 1H), 7.61 (dd, 1H), 8.13 (d, 1H).

15 MS (ESP+): m/e 357/9 (M+H)⁺.

4-(5-bromo-2-pyridyloxy)piperidine



20 Scale: 4.99g, 24.9mmol

Method C. The solvents were evaporated and the residue partitioned between Et₂O and aq. HCl. The aqueous layer was basified with K₂CO₃ and extracted with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and evaporated to give an orange gum.

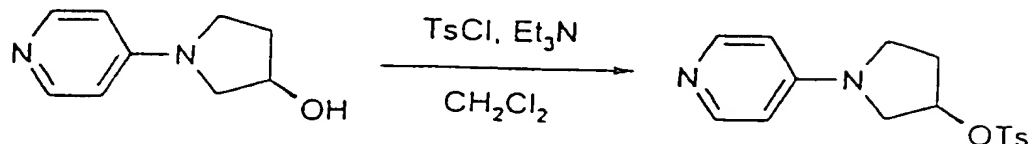
Yield = 380mg (90%)

$R_f = 0.43$ (20%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (250MHz, CDCl₃): $\delta = 1.7$ (m, 2H), 2.05 (m, 2H), 2.77 (m, 2H), 3.14 (m, 2H), 5.08 (m, 1H), 6.61 (d, 1H), 7.66 (dd, 1H), 8.15 (d, 1H).

5 MS (ESP+): m/e 257/9 (M+H)⁺.

(R)-1-(4-pyridyl)-3-(p-toluenesulphonyloxy)pyrrolidine



10

Scale: 1.0 g, 6.1 mmol

Tosyl chloride (1.28g, 1.1 equivalents) was added to a suspension of the alcohol and triethylamine (0.92g, 1.1 equivalents) in dichloromethane (10ml). A solution gradually
15 formed. After stirring overnight, the solution was washed with saturated aqueous sodium bicarbonate solution, dried over sodium sulphate, filtered and evaporated. The residue was purified by column chromatography, eluting sequentially with CH₂Cl₂; 5%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving a light brown solid.

Yield = 1.14 g (58%)

20 $R_f = 0.32$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300 MHz, CDCl₃): $\delta = 2.20$ (m, 1H), 2.33 (m, 1H), 2.45 (s, 3H), 3.45 (m, 4H), 5.21 (m, 1H), 6.32 (d, 2H), 7.38 (d, 2H), 7.79 (d, 2H), 8.20 (d, 2H).

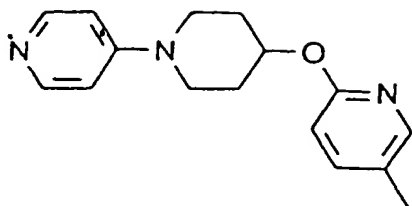
MS (ESP+): m/e 319 (M+H)⁺.

The (S) enantiomer was made by an identical protocol starting from the (S) alcohol.

25

Example 64

1-(4-pyridyl)-4-(5-methyl-2-pyridyloxy)piperidine



Scale: 500mg, 2.8mmol

Method B, using 1-(4-pyridyl)-4-hydroxypiperidine and 2-bromo-5-methylpyridine. The crude product was purified by column chromatography on silica, eluting with CH_2Cl_2 , then Et_2O , then

10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$. The product was isolated as an orange solid.

Yield = 349mg (46%)

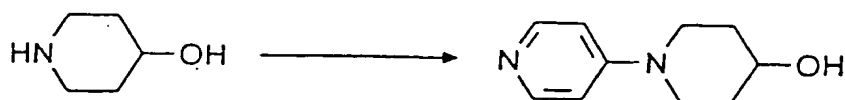
R_f = 0.58 (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 1.83 (m, 2H), 2.06 (m, 2H), 2.22 (s, 3H), 3.3 (m, 2H), 3.65 (m, 2H), 5.25 (m, 1H), 6.65 (m, 3H), 7.38 (dd, 1H), 7.92 (m, 1H), 8.25 (dd, 2H).

MS (CI): m/e 270 ($\text{M}+\text{H}$) $^+$.

Found: C, 70.9; H, 7.1; N, 15.3; $\text{C}_{16}\text{H}_{19}\text{N}_3\text{O}$ requires: C 71.3; H, 7.11; N, 15.6%.

15 The 1-(4-pyridyl)-4-hydroxypiperidine was prepared as follows:



Scale: 26.9g, 0.266mol

20

Method A, using 4-hydroxypiperidine. Work-up: the pH was adjusted to 14 with aq. NaOH. The solid product was filtered, taken up with H_2O & pH adjusted to 8.5. The solid product was filtered, dissolved in MeOH & preadsorbed onto silica. Column chromatography, eluting with 10%MeOH/ CH_2Cl_2 and increasing to 20%MeOH/5% $\text{PrNH}_2/\text{CH}_2\text{Cl}_2$ gave the product as a sticky solid.

25

Yield 22.25g (47%).

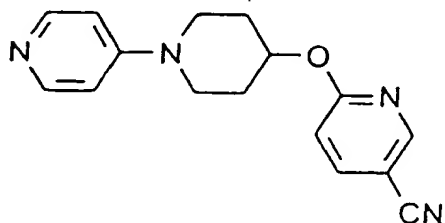
R_f = 0.25 (20%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

¹H-NMR (DMSO-d₆): δ = 1.4 (m, 2H), 1.6 (m, 2H), 3.05 (m, 2H), 3.5 (m, 3H), 6.6 (m, 2H), 8.1 (m, 2H).

MS (ESP+): m/e 179.5 (M+H)⁺.

5 Example 65

1-(4-pyridyl)-4-(5-cyano-2-pyridyloxy)piperidine



10 Scale: 500mg, 2.8mmol

Method B, using 1-(4-pyridyl)-4-hydroxypiperidine and 2-chloro-5-cyanopyridine. The crude product was dissolved in CH₂Cl₂, adsorbed onto silica and purified by column

chromatography, eluting with 10%MeOH/1%NH₄OH/CH₂Cl₂. The residue was further

15 purified by column chromatography, eluting with 5%MeOH/1%NH₄OH/CH₂Cl₂. The residue was suspended in ethyl acetate and a solution of dry HCl in ether added. The hydrochloride salt was filtered off and suspended in water. The pH was adjusted to 14 with aq NaOH and the product extracted into ethyl acetate/methanol (ca. 10:1). The organic phase was washed with brine. After evaporation, the product was triturated with ether, giving an orange solid.

20 Yield = 48mg (6%)

R_f = 0.58 (10%MeOH/1%NH₄OH/CH₂Cl₂)

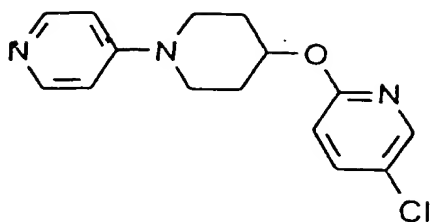
¹H-NMR (200MHz, CDCl₃): δ = 1.9 (m, 2H), 2.12 (m, 2H), 3.3 (m, 2H), 3.7 (m, 2H), 5.38 (m, 1H), 6.7 (m, 2H), 6.8 (d, 1H), 7.8 (dd, 1H), 8.3 (m, 2H), 8.48 (m, 1H).

MS (ESP+): m/e 281 (M+H)⁺.

25

Example 66

1-(4-pyridyl)-4-(5-chloro-2-pyridyloxy)piperidine



Scale: 500mg, 2.8mmol

Method B, using 1-(4-pyridyl)-4-hydroxypiperidine and 2,5-dichloropyridine. The reaction mixture was partitioned between aq. HCl and CH₂Cl₂. The aqueous phase was adjusted to pH 14 with aq. NaOH and extracted with CH₂Cl₂. The organic phase was washed with brine, dried over anhydrous Na₂SO₄ and evaporated. The residue was purified by column chromatography on silica eluting with CH₂Cl₂, then Et₂O, then 5%MeOH/1%NH₄OH/CH₂Cl₂ to give the product as a white solid.

10 Yield = 303mg (38%)

$R_f = 0.5$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

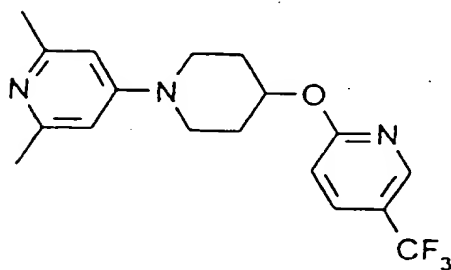
¹H-NMR (200MHz, CDCl₃): δ = 1.9 (m, 2H), 2.1 (m, 2H), 3.3 (m, 2H), 3.68 (m, 2H), 5.25 (m, 1H), 6.7 (m, 3H), 7.53 (dd, 1H), 8.07 (m, 1H), 8.28 (m, 2H).

MS (CI): m/e 290 (M+H)⁺.

15

Example 67

1-(2,6-dimethyl-4-pyridyl)-4-(5-trifluoromethyl-2-pyridyloxy)piperidine



20

Scale: 300mg, 1.22mmol

Method A. using 2,6-dimethyl-4-chloropyridine (see T. Kato, H. Hayashi & T. Anzai; *Chem. Pharm. Bull.*; 15, 1967, 1343-1348) and 4-(5-trifluoromethyl-2-pyridyloxy)piperidine in a water/n-propanol (1:10) solvent mixture. The solvents were evaporated and the residue purified by column chromatography on silica, eluting with CH_2Cl_2 , then

5 5%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, then 10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, giving the product as a yellow glass.

Yield = 171mg (40%)

R_f = 0.36 (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

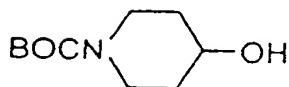
$^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 2.0 (m, 2H), 2.1 (m, 2H), 2.6 (s, 6H), 3.6 (m, 2H), 3.8 (m, 10 2H), 5.48 (m, 1H), 6.46 (s, 2H), 6.84 (d, 1H), 7.8 (dd, 1H), 8.07 (m, 1H), 8.42 (m, 1H).

MS(ESP+): m/e 352 (M+H) $^+$.

The precursor 4-(5-trifluoromethyl-2-pyridyloxy)piperidine was made in three steps from 4-hydroxypiperidine as follows:

15

1) 1-(t-butoxycarbonyl)-4-hydroxypiperidine



20

Scale: 44.14g, 0.44mol

4-Hydroxypiperidine (44.14g, 0.44mol) was suspended in CH_2Cl_2 (150ml) and cooled in an ice-bath. A solution of di-t-butyl dicarbonate (100g, 0.46mol) in CH_2Cl_2 (110ml) was added

25 slowly. After stirring overnight the product was partitioned between water and CH_2Cl_2 . The organic layer was washed with brine and dried over anhydrous magnesium sulphate.

Filtration and evaporation gave the product as a white solid.

Yield 95g (quantitative, crude).

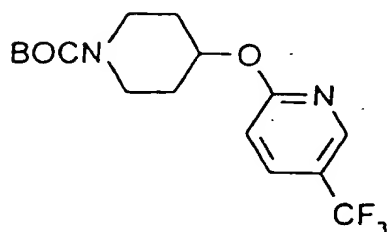
R_f = 0.18 (20% EtOAc/ CH_2Cl_2)

30 $^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 1.45 (s, 9H), 1.43 (m, 2H), 1.85 (m, 2H), 3.04 (m, 2H), 4.85 (m, 1H).

MS (CI+): m/e 201 (M+H)⁺.

2) 1-(t-butoxycarbonyl)-4-(5-(trifluoromethyl)-2-pyridyloxy)piperidine

5



Scale: 4.99g, 24.9mmol

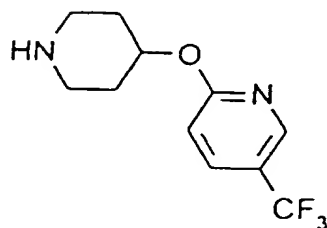
Method B, using 1-(t-butyloxycarbonyl)-4-hydroxypiperidine and 2-bromo-5-
10 trifluoromethylpyridine. The crude product was partially purified by column chromatography on silica, eluting with EtOAc/hexane (0% to 25% in increments of 5%).

R_f = 0.42 (20%EtOAc/hexane)

15 ¹H-NMR (200MHz, CDCl₃): δ = 1.48 (s, 9H), 1.75 (m, 2H), 2.0 (m, 2H), 3.3 (m, 2H), 3.78 (m, 2H), 5.3 (m, 1H), 6.78 (d, 1H), 7.77 (dd, 1H), 8.4 (s, 1H).

MS (ESP+): m/e 347 (M+H)⁺.

20 3) 4-(5-(trifluoromethyl)-2-pyridyloxy)piperidine



Scale: 9.2g (impure), ca. 25mmol

Method C. The solvents were evaporated and the residue partitioned between CH_2Cl_2 and aq. K_2CO_3 . The organic phase was dried over anhydrous Na_2SO_4 and evaporated to give an orange gum. After trituration with Et_2O the product was isolated as an off-white solid. Yield = 3.58g (55%)

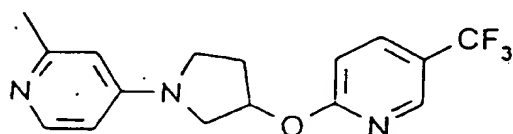
5 $R_f = 0.19$ (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (250MHz, CDCl_3): $\delta = 1.7$ (m, 2H), 2.1 (m, 2H), 2.85 (m, 2H), 3.15 (m, 2H), 5.25 (m, 1H), 6.75 (d, 1H), 7.75 (dd, 1H), 8.4 (d, 1H).

MS (ESP+): m/e 247 (M+H) $^+$.

10 Example 68

1-(2-methyl-4-pyridyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



15 Scale: 500mg, 2.16mmol

Method A, using 2-methyl-4-chloropyridine (see T. Kato, H. Hayashi & T. Anzai: *Chem. Pharm. Bull.*: 15, 1967, 1343-1348) and 3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine. The solvents were evaporated and the residue was purified by column chromatography on silica.

20 eluting with Et_2O , then EtOAc, then 5%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, then 10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, giving the product as a white foam.

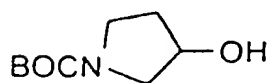
Yield = 175mg (25%)

$R_f = 0.35$ (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (200MHz, CDCl_3): $\delta = 2.45$ (m, 2H), 2.65 (s, 3H), 3.68 (m, 3H), 3.75 (dd, 1H), 5.83 (m, 1H), 6.35 (m, 1H), 6.47 (dd, 1H), 6.84 (d, 1H), 7.82 (dd, 1H), 8.07 (d, 1H), 8.45 (m, 1H).

MS (ESP+): m/e 324 (M+H) $^+$.

The precursor 3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine was made in three steps from 3-hydroxypyrrolidine as follows:

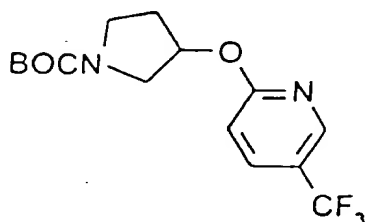
1) 1-(t-butoxycarbonyl)-3-hydroxypyrrolidine

Scale: 5.0g, 57.0mmol

5

A solution of 3-hydroxypyrrolidine (5.0g, 57.0mmol) in CH_2Cl_2 (125ml) was added to an ice-cold solution of di-*t*-butyl dicarbonate (13.15g, 60mmol) in CH_2Cl_2 (125ml). After stirring overnight the solvents were evaporated and the residue purified by column chromatography on silica, eluting with CH_2Cl_2 , then Et_2O , then EtOAc, giving the product as a white solid.

10 Yield 10.4g (98%).

 $R_f = 0.23$ (Et_2O) $^1\text{H-NMR}$ (250MHz, CDCl_3): $\delta = 1.42$ (s, 9H), 2.0 (m, 3H), 3.4 (m, 3H), 4.4 (m, 1H). MS (CI^+): m/e 188 ($\text{M}+\text{H}$) $^+$.15 2) 1-(t-butoxycarbonyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine

Scale: 4.99g, 24.9mmol

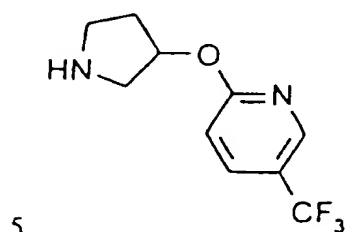
20 Method B, using 1-(*t*-butoxycarbonyl)-3-hydroxypyrrolidine and 2-bromo-5-trifluoromethylpyridine. The crude product was partially purified by column chromatography on silica, eluting with 10% MeOH/ CH_2Cl_2 . Further purification by column chromatography on silica, eluting with 10% Et_2O / CH_2Cl_2 , gave the product as an oily solid.

Yield 7.44g (83%).

25 $R_f = 0.81$ (10% Et_2O / CH_2Cl_2) $^1\text{H-NMR}$ (200MHz, CDCl_3): $\delta = 1.48$ (s, 9H), 2.2 (m, 2H), 3.6 (m, 4H), 5.6 (m, 1H), 6.6 (d, 1H), 7.77 (dd, 1H), 8.42 (s, 1H).

MS (ESP+): m/e 333 (M+H)⁺.

3) 3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



Scale: 7.34g, 22mmol

Method C. The solvents were evaporated and the residue partitioned between Et₂O and aq. HCl. The aqueous layer was basified with K₂CO₃ and extracted with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and evaporated to give an orange gum.

Yield = 3.3g (64%)

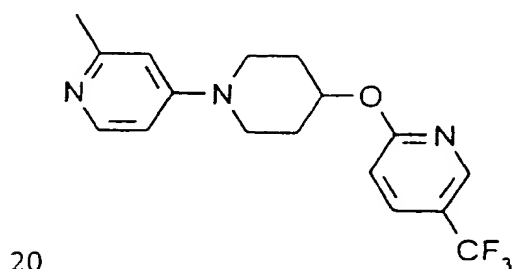
R_f = 0.83 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): δ = 1.95 (m, 1H), 2.15 (m, 1H), 2.95 (m, 1H), 3.16 (m, 3H), 5.53 (m, 1H), 6.78 (d, 1H), 7.74 (dd, 1H), 8.42 (m, 1H).

15 MS (ESP+): m/e 233 (M+H)⁺.

Example 69

1-(2-methyl-4-pyridyl)-4-(5-trifluoromethyl-2-pyridyloxy)piperidine



Scale: 300mg, 1.22mmol

Method A. using 2-methyl-4-chloropyridine and 4-(5-trifluoromethyl-2-pyridyloxy)piperidine. The solvents were evaporated and the residue was purified by column

chromatography on silica, eluting with Et₂O, then EtOAc, then

5%MeOH/1%NH₄OH/CH₂Cl₂, then 10%MeOH/1%NH₄OH/CH₂Cl₂, giving the product as a yellow oil.

Yield = 76mg (18%)

5 R_f = 0.54 (10%MeOH/1%NH₄OH/CH₂Cl₂)

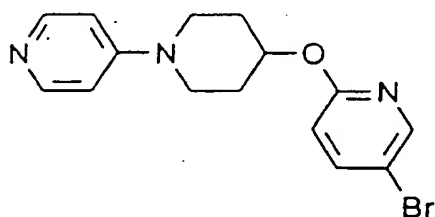
¹H-NMR (200MHz, CDCl₃): δ = 2.0 (m, 2H), 2.15 (m, 2H), 2.6 (s, 3H), 3.6 (m, 2H), 3.8 (m, 2H), 5.48 (m, 1H), 6.6 (m, 1H), 6.72 (dd, 1H), 6.82 (d, 1H), 7.8 (dd, 1H), 8.25 (d, 1H), 8.43 (m, 1H).

MS (ESP+): m/e 338 (M+H)⁺.

10

Example 70

1-(4-pyridyl)-4-(5-bromo-2-pyridyloxy)piperidine



15 Scale: 360mg, 1.4mmol

Method A, using 4-(5-bromo-2-pyridyloxy)piperidine. The solvents were evaporated and the residue partitioned between CH₂Cl₂ and aq. K₂CO₃. The organic phase was dried over anhydrous Na₂SO₄ and evaporated. The residue was purified by column chromatography on silica, eluting from 1%MeOH/1%NH₄OH/CH₂Cl₂ to 10%MeOH/1%NH₄OH/CH₂Cl₂ (in 1% increments), giving the product as a white solid.

Yield = 285mg (61%)

R_f = 0.61 (20%MeOH/1%NH₄OH/CH₂Cl₂)

25 ¹H-NMR (200MHz, CDCl₃): δ = 1.85 (m, 2H), 2.08 (m, 2H), 3.32 (m, 2H), 3.65 (m, 2H), 5.25 (m, 1H), 6.65 (m, 3H), 7.65 (dd, 1H), 8.17 (d, 1H), 8.25 (m, 2H).

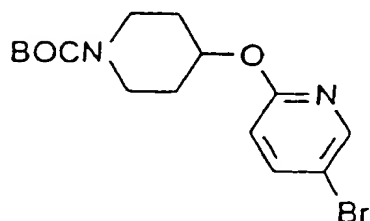
MS (CI+): m/e 334 (M+H)⁺.

Found: C, 53.0; H, 4.7; N, 12.2; $C_{15}H_{16}BrN_3O \cdot (0.25H_2O)$ requires: C 53.1; H, 5.06; N, 12.4%.

The precursor 4-(5-bromo-2-pyridyloxy)piperidine was prepared in two steps from 1-(t-butoxycarbonyl)-4-hydroxypiperidine as follows:

5

1) 1-(t-butoxycarbonyl)-4-(5-bromo-2-pyridyloxy)piperidine



Scale: 0.79g, 3.93mmol

10

Method: under argon, 1-(t-butoxycarbonyl)-4-hydroxypiperidine (0.79 g, 3.93 mmol), 5-bromo-2-pyridone (0.49 g, 3.02 mmol) and triphenylphosphine (1.14 g, 4.35 mmol) were dissolved in THF (20 ml). To the mixture was added diisopropylazodicarboxylate (0.91 ml, 4.62 mmol) dropwise at ambient temperature followed by stirring for 18 hours. The mixture was concentrated *in vacuo* and applied to the top of a silica column. Elution with solvent of increasing concentration of EtOAc in CH_2Cl_2 and evaporation *in vacuo* of the relevant fractions gave the product.

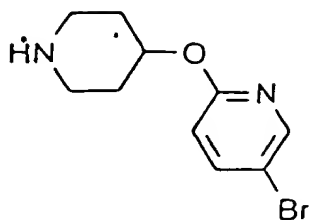
Yield = 640mg (61%)

20 $R_f = 0.63$ (EtOAc)

1H -NMR (200MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H), 1.7 (m, 2H), 1.92 (m, 2H), 3.25 (m, 2H), 3.75 (m, 2H), 5.15 (m, 1H), 6.61 (d, 1H), 7.61 (dd, 1H), 8.13 (d, 1H).

MS (ESP+): m/e 357/9 ($M+H$) $^+$.

25 2) 4-(5-bromo-2-pyridyloxy)piperidine



Scale: 4.99g, 24.9mmol

Method C. The solvents were evaporated and the residue partitioned between Et₂O and aq. 5 HCl. The aqueous layer was basified with K₂CO₃ and extracted with CH₂Cl₂. The organic phase was dried over anhydrous Na₂SO₄ and evaporated to give an orange gum.

Yield = 380mg (90%)

R_f = 0.43 (20%MeOH/1%NH₄OH/CH₂Cl₂)

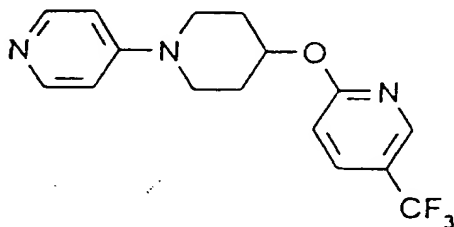
¹H-NMR (250MHz, CDCl₃): δ = 1.7 (m, 2H), 2.05 (m, 2H), 2.77 (m, 2H), 3.14 (m, 2H), 5.08 10 (m, 1H), 6.61 (d, 1H), 7.66 (dd, 1H), 8.15 (d, 1H).

MS (ESP+): m/e 257/9 (M+H)⁺.

Example 71

1-(4-pyridyl)-4-(5-trifluoromethyl-2-pyridyloxy)piperidine

15



Scale: 714mg, 4mmol

Method B, using 1-(4-pyridyl)-4-hydroxypiperidine and 2-bromo-5-trifluoromethylpyridine. The solvents were evaporated and the residue was purified by column chromatography on 20 silica, eluting from 1%MeOH/1%iPrNH₂/CH₂Cl₂ to 5%MeOH/5%iPrNH₂/CH₂Cl₂ (in 1% increments). A second column, eluting with 1%MeOH/1%NH₄OH/CH₂Cl₂ to 10%MeOH/1%NH₄OH/CH₂Cl₂ (in 1% increments), gave a dark oil, which was extracted with Et₂O/hexane. Evaporation and washing with hexane gave the product as a light brown solid. Yield = 674mg (52%)

$R_f = 0.52$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

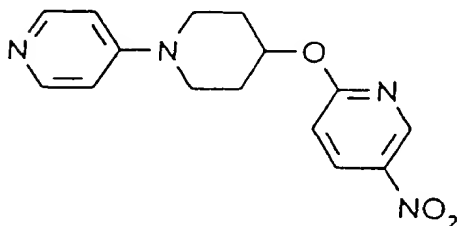
¹H-NMR (200MHz, CDCl₃): $\delta = 1.9$ (m, 2H), 2.1 (m, 2H), 3.32 (m, 2H), 3.68 (m, 2H), 5.38 (m, 1H), 6.70 (d, 2H), 6.62 (d, 2H), 7.77 (dd, 1H), 8.27 (d, 2H), 8.44 (s, 1H).

MS (ESP+): m/e 324 (M+H)⁺.

5 Found: C,57.7; H,5.1; N,12.4; C₁₆H₁₆F₃N₃O.(0.5H₂O) requires: C,57.8; H,5.15; N,12.64%.

Example 72

1-(4-pyridyl)-4-(5-nitro-2-pyridyloxy)piperidine



10

Scale: 433mg, 2.43mmol

Method B, using 1-(4-pyridyl)-4-hydroxypiperidine and 2-bromo-5-nitropyridine. The solvents were evaporated and the residue was columned on silica, eluting from

15 1%MeOH/1%NH₄OH/CH₂Cl₂ to 10%MeOH/1%NH₄OH/CH₂Cl₂ (in 1% increments), giving a brown solid. After recrystallisation from methyl t-butyl ether, the product was isolated as an orange solid.

Yield = 70mg (10%)

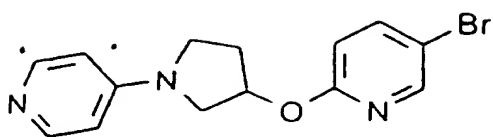
$R_f = 0.39$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

20 ¹H-NMR (200MHz, CDCl₃): $\delta = 1.9$ (m, 2H), 2.15 (m, 2H), 3.33 (m, 2H), 3.68 (m, 2H), 5.45 (m, 1H), 6.70 (dd, 2H), 6.82 (d, 1H), 8.28 (dd, 2H), 8.35 (dd, 1H), 9.06 (d, 1H).

MS (ESP+): m/e 301 (M+H)⁺.

Example 73

25 1-(4-pyridyl)-3-(5-bromo-2-pyridyloxy)pyrrolidine



Scale: 492mg, 3mmol

5 Method B. using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2,5-dibromopyridine. The crude residue was recrystallised from methyl t-butyl ether.

Yield = 620mg (65%)

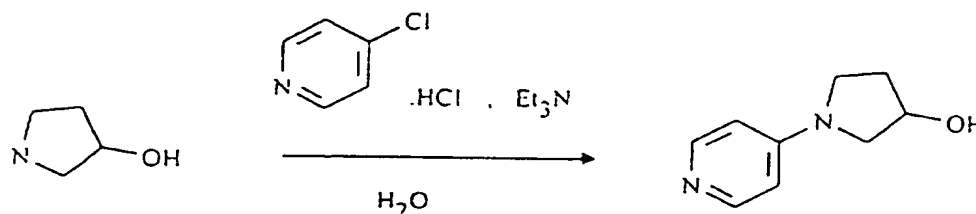
$R_f = 0.41$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

10 ¹H-NMR (300MHz, CDCl₃): δ = 2.35 (m, 2H), 3.5 (m, 3H), 3.72 (dd, 1H), 5.65 (m, 1H), 6.38 (m, 2H), 6.62 (d, 1H), 7.64 (dd, 1H), 8.2 (m, 3H).

MS (ESP+): m/e 320/2 (M+H)⁺.

Found: C,52.9; H,4.6; N,12.8; C₁₄H₁₄BrN₃O requires: C52.5; H,4.41; N,13.1%.

15 The precursor 1-(4-pyridyl)-3-hydroxypyrrolidine was prepared as follows:



20

Scale: 5g, 57.4mmol

Method A. Work-up: the reaction mixture was cooled in an ice bath for 1 hour. The resultant white solid was filtered off and washed with ice water (30 ml) and dried overnight *in vacuo* in
25 the presence of silica gel. The product was given as fine white powder.

Yield 5.78g (61%).

• $R_f = 0.1$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

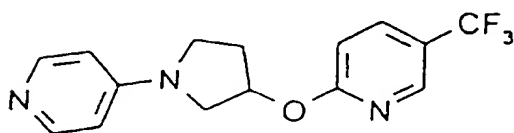
¹H-NMR (200MHz, DMSO-d₆): $\delta = 2.0$ (m, 2H), 3.22 (m, 1H), 3.7 (m, 3H), 4.4 (m, 1H), 5.0 (s, OH), 6.32 (m, 2H), 8.15 (m, 2H).

MS (ESP+): m/e 165 (M+H)⁺.

5

Example 74

1-(4-pyridyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



10

Scale: 648mg, 3.95mmol

Method B. using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-bromo-5-trifluoromethylpyridine.
The crude residue was recrystallised from methyl t-butyl ether.

15 Yield = 710mg (58%)

$R_f = 0.28$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

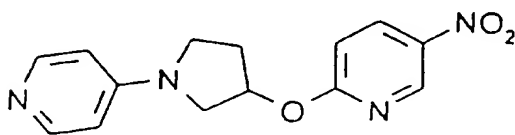
¹H-NMR (300MHz, CDCl₃): $\delta = 2.38$ (m, 2H), 3.55 (m, 3H), 3.75 (dd, 1H), 5.78 (m, 1H), 6.4 (d, 2H), 6.8 (d, 1H), 7.8 (dd, 1H), 8.22 (d, 2H), 8.45 (m, 1H).

MS (ESP+): m/e 310 (M+H)⁺.

20 Found: C,58.5; H,4.7; N,13.3; C₁₅H₁₄F₃N₃O requires: C58.3; H,4.56; N,13.6%.

Example 75

1-(4-pyridyl)-3-(5-nitro-2-pyridyloxy)pyrrolidine



25

Scale: 500mg, 3.05mmol

Method D, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-bromo-5-nitropyridine. The residue was purified by chromatography on silica, eluting from 1%MeOH/1%NH₄OH/CH₂Cl₂ to 10%MeOH/1%NH₄OH/CH₂Cl₂ (in 1% increments). The crude product was recrystallised from EtOAc to give a pale brown solid.

5 Yield = 460mg (53%)

R_f = 0.41 (10%MeOH/1%NH₄OH/CH₂Cl₂)

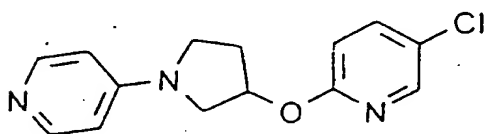
¹H-NMR (300MHz, CDCl₃): δ = 2.4 (m, 2H), 3.58 (m, 3H), 3.8 (dd, 1H), 5.85 (m, 1H), 6.4 (d, 2H), 6.82 (d, 1H), 8.22 (m, 2H), 8.38 (dd, 1H), 9.08 (s, 1H).

MS (ESP+): m/e 287 (M+H)⁺.

10

Example 76

1-(4-pyridyl)-3-(5-chloro-2-pyridyloxy)pyrrolidine



15

Scale: 500mg, 3.05mmol

Method B, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2,5-dichloropyridine. The crude residue was recrystallised from methyl t-butyl ether.

20 Yield = 570mg (68%)

R_f = 0.50 (10%MeOH/1%NH₄OH/CH₂Cl₂)

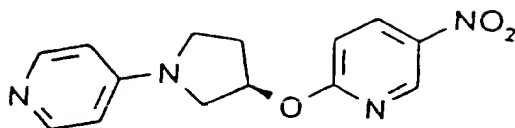
¹H-NMR (300MHz, CDCl₃): δ = 2.35 (m, 2H), 3.5 (m, 3H), 3.7 (dd, 1H), 5.65 (m, 1H), 6.38 (m, 2H), 6.65 (d, 1H), 7.55 (dd, 1H), 8.1 (m, 1H), 8.2 (m, 2H).

MS (ESP+): m/e 276 (M+H)⁺.

25

Example 77

(3R)-1-(4-pyridyl)-3-(5-nitro-2-pyridyloxy)pyrrolidine



Scale: 500mg, 3.05mmol

5 Method D. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-bromo-5-nitropyridine, with 1hr reaction time. The crude product was recrystallised from EtOAc/hexane.

Yield = 480mg (55%)

R_f = 0.41 (10%MeOH/1%NH₄OH/CH₂Cl₂)

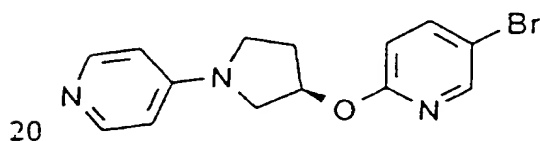
¹H-NMR (300MHz, CDCl₃): δ = 2.4 (m, 2H), 3.58 (m, 3H), 3.8 (dd, 1H), 5.85 (m, 1H), 6.410 (d, 2H), 6.82 (d, 1H), 8.22 (m, 2H), 8.38 (dd, 1H), 9.08 (s, 1H).

MS (ESP+): m/e 287 (M+H)⁺.

The precursor (R)-1-(4-pyridyl)-3-hydroxypyrrolidine was prepared in analogous manner to the racemic material. The NMR spectrum, mass spectrum and R_f were as for the racemate, 15 and the R enantiomer gave an optical rotation (α_D) of -22.5 (c=10mg/ml, MeOH).

Example 78

(3R)-1-(4-pyridyl)-3-(5-bromo-2-pyridyloxy)pyrrolidine



Scale: 500mg, 3.05mmol

Method B. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,5-dibromopyridine. The crude product was recrystallised from EtOAc/hexane.

Yield = 550mg (57%)

R_f = 0.41 (10%MeOH/1%NH₄OH/CH₂Cl₂)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.35 (m, 2H), 3.5 (m, 3H), 3.72 (dd, 1H), 5.65 (m, 1H), 6.38 (m, 2H), 6.62 (d, 1H), 7.64 (dd, 1H), 8.2 (m, 3H).

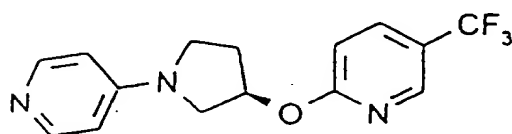
MS (ESP+): m/e 320/2 ($\text{M}+\text{H}$) $^+$.

Found: C,52.9; H,4.5; N,13.1; $\text{C}_{14}\text{H}_{14}\text{BrN}_3\text{O}$ requires: C52.5; H,4.41; N,13.1%.

5

Example 79

(3R)-1-(4-pyridyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



10

Scale: 500mg, 3.05mmol

Method B. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-bromo-5-trifluoromethylpyridine. The crude product was recrystallised from EtOAc/hexane.

15 Yield = 230mg (24%)

R_f = 0.39 (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

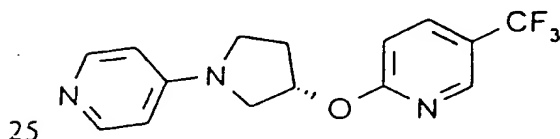
$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.38 (m, 2H), 3.55 (m, 3H), 3.75 (dd, 1H), 5.78 (m, 1H), 6.4 (d, 2H), 6.8 (d, 1H), 7.8 (dd, 1H), 8.22 (d, 2H), 8.45 (m, 1H).

MS (ESP+): m/e 310 ($\text{M}+\text{H}$) $^+$.

20 Found: C,58.6; H,4.8; N,13.4; $\text{C}_{15}\text{H}_{14}\text{F}_3\text{N}_3\text{O}$ requires: C58.3; H,4.56; N,13.6%.

Example 80

(3S)-1-(4-pyridyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



25

Scale: 500mg, 3.05mmol

- Method B, using (S)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-bromo-5-trifluoromethylpyridine. The crude product was recrystallised from EtOAc/hexane.

Yield = 300mg (32%)

R_f = 0.39 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): δ = 2.38 (m, 2H), 3.53 (m, 3H), 3.76 (dd, 1H), 5.78 (m, 1H), 6.4 (d, 2H), 6.8 (d, 1H), 7.8 (dd, 1H), 8.2 (d, 2H), 8.45 (m, 1H).

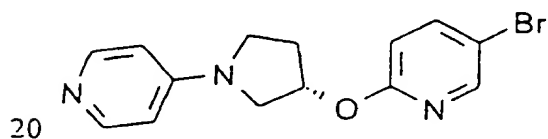
MS (ESP+): m/e 310 (M+H)⁺.

Found: C, 57.7; H, 4.6; N, 13.2; C₁₅H₁₄F₃N₃O.(0.16H₂O) requires: C 57.7; H, 4.62; N, 13.46%.

- 10 The precursor (S)-1-(4-Pyridyl)-3-hydroxypyrrolidine was made by the method used for racemic material. The NMR spectrum, mass spectrum and R_f were as for the racemate, and the S enantiomer gave an optical rotation (α_D) of +22.7 (c=10mg/ml, MeOH). The starting (S)-3-hydroxypyrrolidine was made from (S)-1-benzyl-3-hydroxypyrrolidine (Fluorochem) by hydrogenolysis of the benzyl group (M.M. Bowers Nemia, J. Lee and M.M. Joullie: *Synth. Comm.*, 1983, 13, 117-1123)

Example 81

(3S)-1-(4-pyridyl)-3-(5-bromo-2-pyridyloxy)pyrrolidine



Scale: 500mg, 3.05mmol

- Method B, using (S)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,5-dibromopyridine. The crude product was recrystallised from EtOAc/hexane.

Yield = 476mg (49%)

R_f = 0.41 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): δ = 2.35 (m, 2H), 3.5 (m, 3H), 3.72 (dd, 1H), 5.65 (m, 1H), 6.38 (m, 2H), 6.62 (d, 1H), 7.64 (dd, 1H), 8.2 (m, 3H).

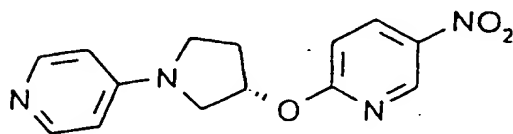
MS (ESP+): m/e 320/2 (M+H)⁺.

Found: C, 52.5; H, 4.5; N, 12.9; $C_{14}H_{14}BrN_3O$ requires: C, 52.5; H, 4.41; N, 13.1%.

Example 82

(3S)-1-(4-pyridyl)-3-(5-nitro-2-pyridyloxy)pyrrolidine

5



Scale: 500mg, 3.05mmol

10 Method D. using (S)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-bromo-5-nitropyridine, with 1hr reaction time. The crude product was recrystallised from methyl t-butyl ether, giving a pale yellow powder.

Yield = 150mg (17%)

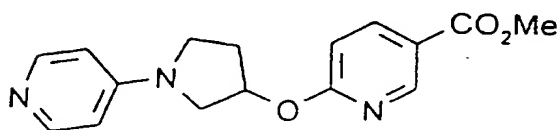
R_f = 0.41 (10%MeOH/1% NH_4OH/CH_2Cl_2)

15 1H -NMR (200MHz, $CDCl_3$): δ = 2.4 (m, 2H), 3.55 (m, 3H), 3.8 (dd, 1H), 5.85 (m, 1H), 6.42 (m, 2H), 6.82 (d, 1H), 8.22 (m, 2H), 8.38 (dd, 1H), 9.08 (d, 1H).

MS (ESP+): m/e 287 (M+H) $^+$.

Example 83

20 1-(4-pyridyl)-3-(5-methoxycarbonyl-2-pyridyloxy)pyrrolidine



Scale: 2.0g, 12.2mmol

25

Method D. using 1-(4-pyridyl)-3-hydroxypyrrolidine and methyl 6-chloronicotinate. The crude product was recrystallised from aqueous ethanol.

Yield = 2.43g (67%)

$R_f = 0.31$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): $\delta = 2.38$ (m, 2H), 3.53 (m, 3H), 3.75 (dd, 1H), 3.92 (s, 3H), 5.81 (m, 1H), 6.4 (d, 2H), 6.72 (d, 1H), 8.16 (m, 3H), 8.82 (m, 1H).

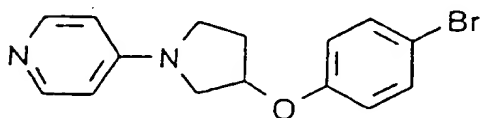
MS (ESP+): m/e 300 (M+H)⁺.

5 Found: C,60.7; H,5.6; N,13.0; C₁₆H₁₇N₃O₃·(H₂O) requires: C60.5; H,6.0; N,13.2%.

Example 84

1-(4-pyridyl)-3-(4-bromophenyl)pyrrolidine

10



Scale: 2.44mmol

15 Method E. using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-bromophenol. The product was further purified by recrystallisation from MTBE, giving a white solid.

Yield = 187mg (24%)

$R_f = 0.49$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

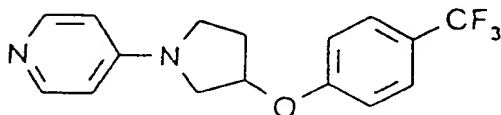
¹H-NMR (200MHz, CDCl₃): $\delta = 2.3$ (m, 2H), 3.5 (m, 3H), 3.65 (m, 1H), 5.05 (m, 1H), 6.4 (dd, 2H), 6.78 (dd, 2H), 7.42 (dd, 2H), 8.25 (dd, 2H).

MS (CI): m/e 319 (M+H)⁺.

Found: C,56.5; H,4.7; N,8.7; C₁₅H₁₅BrN₂O requires: C56.4; H,4.74; N,8.78%.

Example 85

25 1-(4-pyridyl)-3-(4-(trifluoromethyl)phenyl)pyrrolidine



Scale: 2.44mmol

Method E. using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-trifluoromethylphenol. The product was further purified by trituration with hexane, giving a white solid.

Yield = 278mg (37%)

$R_f = 0.44$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): δ = 2.35 (m, 2H), 3.55 (m, 3H), 3.72 (dd, 1H), 5.14 (m, 1H), 6.4 (dd, 2H), 6.96 (dd, 2H), 7.60 (dd, 2H), 8.25 (dd, 2H).

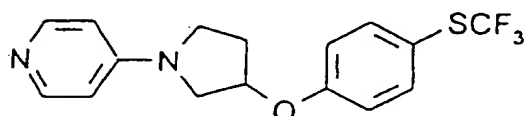
MS (CI): m/e 309 (M+H)⁺.

Found: C,62.0; H,5.0; N,9.1; C₁₆H₁₃F₃N₂O requires: C62.3; H,4.90; N,9.09%.

Example 86

1-(4-pyridyl)-3-(4-(trifluoromethylthio)phenyloxy)pyrrolidine

15



Scale: 2.44mmol

20

Method E. using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-(trifluoromethylthio)phenol. The product was further purified by trituration with diethyl ether, giving a white solid.

Yield = 50mg (6%)

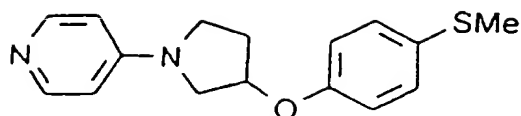
$R_f = 0.42$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): δ = 2.48 (m, 2H), 3.77 (m, 3H), 3.92 (dd, 1H), 5.22 (m, 1H), 6.68 (d, 2H), 6.92 (d, 2H), 7.61 (d, 2H), 8.16 (d, 2H).

MS (CI): m/e 341 (M+H)⁺.

Example 87

30 1-(4-pyridyl)-3-(4-(methylthio)phenyloxy)pyrrolidine



5 Scale: 3.21mmol

Method E, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-(methylthio)phenol. The product was further purified by recrystallisation from MTBE, giving a white powder.

Yield = 183mg (37%)

10 $R_f = 0.32$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): δ = 2.25 (m, 1H), 2.36 (m, 1H), 2.44 (s, 3H), 3.52 (m, 3H), 3.64 (dd, 1H), 5.04 (m, 1H), 6.4 (d, 2H), 6.82 (d, 2H), 7.24 (d, 2H), 8.22 (d, 2H).

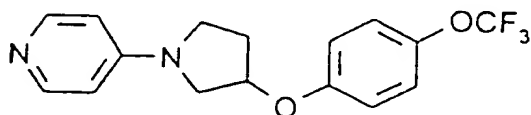
MS (CI): m/e 287 (M+H)⁺.

Found: C, 67.3; H, 6.4; N, 9.7; C₁₆H₁₈N₂OS requires: C, 67.1; H, 6.34; N, 9.78%.

15

Example 88

1-(4-pyridyl)-3-(4-(trifluoromethoxy)phenoxy)pyrrolidine



20

Scale: 2.44mmol

Method E, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-(trifluoromethoxy)phenol. The product was further purified by trituration with hexane, giving a white powder.

Yield = 325mg (41%)

$R_f = 0.32$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

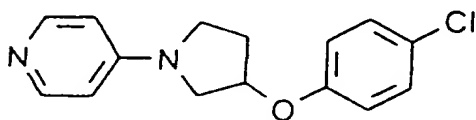
¹H-NMR (300MHz, CDCl₃): δ = 2.28 (m, 1H), 2.38 (m, 1H), 3.52 (m, 3H), 3.64 (dd, 1H), 5.04 (m, 1H), 6.4 (d, 2H), 6.85 (d, 2H), 7.18 (d, 2H), 8.22 (d, 2H).

MS (CI): m/e 325 (M+H)⁺.

Found: C, 59.1; H, 4.8; N, 8.9; C₁₆H₁₅F₃N₂O requires: C 59.3; H, 4.66; N, 8.64%.

Example 89

5 1-(4-pyridyl)-3-(4-chlorophenoxy)pyrrolidine



10 Scale: 2.44mmol

Method E, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-chlorophenol. The product was further purified by recrystallisation from MTBE, giving a white solid.

Yield = 302mg (45%)

15 R_f = 0.33 (10% MeOH/1% NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): δ = 2.25 (m, 1H), 2.38 (m, 1H), 3.5 (m, 3H), 3.64 (dd, 1H), 5.02 (m, 1H), 6.38 (d, 2H), 6.82 (d, 2H), 7.24 (d, 2H), 8.22 (d, 2H).

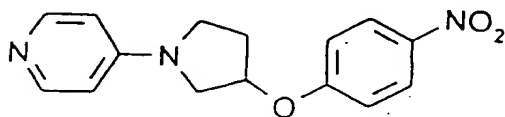
MS (CI): m/e 275 (M+H)⁺.

Found: C, 65.4; H, 5.6; N, 10.1; C₁₅H₁₅ClN₂O requires: C 65.6; H, 5.50; N, 10.2%.

20

Example 90

1-(4-pyridyl)-3-(4-nitrophenoxy)pyrrolidine



25

Scale: 1.83mmol

- Method D, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 4-bromonitrobenzene. The product was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 7% $\text{MeOH}/\text{CH}_2\text{Cl}_2$; 7% $\text{MeOH}/1\%\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$; 10% $\text{MeOH}/1\%\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, giving a brown foam.

5 Yield = 71mg (14%)

$R_f = 0.41$ (10% $\text{MeOH}/1\%\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (300MHz, CDCl_3): $\delta = 2.4$ (m, 2H), 3.6 (m, 3H), 3.78 (dd, 1H), 5.0 (m, 1H), 6.42 (d, 2H), 6.98 (d, 2H), 8.22 (d, 4H).

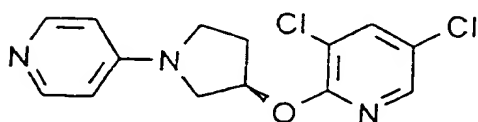
MS (CI): m/e 285 ($\text{M}+\text{H}$) $^+$.

10

Example 91

(3R)-1-(4-pyridyl)-3-(3,5-dichloro-2-pyridyloxy)pyrrolidine

15



Scale: 1.83mmol

- Method B, using (3R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,3,5-trichloropyridine. The product was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 7% $\text{MeOH}/\text{CH}_2\text{Cl}_2$; 7% $\text{MeOH}/1\%\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$; 10% $\text{MeOH}/1\%\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$, giving a brown foam.

Yield = 494mg (87%)

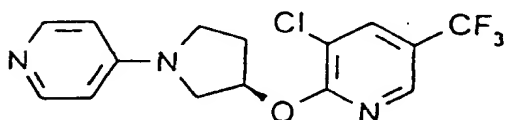
$R_f = 0.31$ (10% $\text{MeOH}/1\%\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

- 25 $^1\text{H-NMR}$ (300MHz, CDCl_3): $\delta = 2.4$ (m, 2H), 3.55 (m, 3H), 3.78 (dd, 1H), 5.68 (m, 1H), 6.42 (d, 2H), 7.63 (d, 1H), 8.02 (s, 1H), 8.22 (d, 2H).

MS (CI): m/e 310/312/314 ($\text{M}+\text{H}$) $^+$.

Found: C, 52.8; H, 4.2; N, 13.2; $\text{C}_{14}\text{H}_{13}\text{Cl}_2\text{N}_3\text{O} \cdot (0.4\text{H}_2\text{O})$ requires: C 52.9; H, 4.38; N, 13.24%.

30 Example 92

(3R)-1-(4-pyridyl)-3-(3,5-dichloro-2-pyridyloxy)pyrrolidine

5

Scale: 1.83mmol

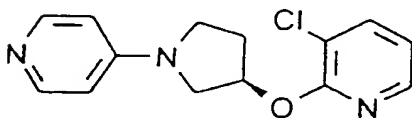
Method B. using (3R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,3-dichloro-5-trifluoromethylpyridine. The product was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 7% MeOH/ CH_2Cl_2 ; 7%MeOH/1% NH_4OH / CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 , giving a brown gum which was further purified by trituration with ether.

Yield = 69mg (11%)

 R_f = 0.36 (10%MeOH/1% NH_4OH / CH_2Cl_2)

15

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.55 (m, 2H), 3.8 (m, 3H), 3.96 (dd, 1H), 5.86 (m, 1H), 6.65 (d, 2H), 7.9 (s, 1H), 8.18 (d, 2H), 8.36 (s, 1H).

MS (CI): m/e 344/346 ($\text{M}+\text{H}$) $^+$.20 Example 93(3R)-1-(4-pyridyl)-3-(3-chloro-2-pyridyloxy)pyrrolidine

25

Scale: 1.83mmol

Method B. using (3R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,3-dichloropyridine. The product was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 7%

MeOH/CH₂Cl₂; 7%MeOH/1%NH₄OH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂, giving an off-white solid which was further purified by recrystallisation from MTBE.

Yield = 303mg (60%)

R_f = 0.47 (10%MeOH/1%NH₄OH/CH₂Cl₂)

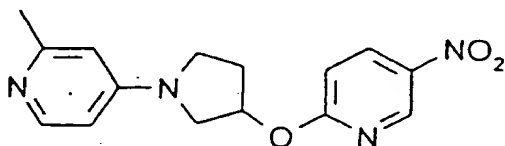
¹H-NMR (300MHz, CDCl₃): δ = 2.4 (m, 2H), 3.55 (m, 3H), 3.78 (dd, 1H), 5.75 (m, 1H), 6.4 (d, 2H), 6.85 (dd, 1H), 7.62 (d, 1H), 8.02 (m, 1H), 8.2 (d, 2H).

MS (CI): m/e 276/278 (M+H)⁺.

Found: C,61.0; H,5.1; N,15.4; C₁₄H₁₄ClN₃O requires: C61.0; H,5.12; N,15.2%.

10 Example 94

1-(2-methyl-4-pyridyl)-3-(5-nitro-2-pyridyloxy)pyrrolidine



Scale: 318mg, 1.76mmol

15

Method A, using 2-methyl-4-chloropyridine and 3-(5-nitro-2-pyridyloxy)pyrrolidine (made in an analogous manner to 3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine above). The solvents were evaporated and the residue was purified by column chromatography on silica, eluting with Et₂O, then EtOAc, then 5%MeOH/1%NH₄OH/CH₂Cl₂, then

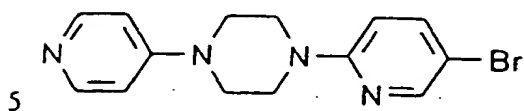
20 10%MeOH/1%NH₄OH/CH₂Cl₂, giving the product as a yellow gum which was triturated with ether, giving a hygroscopic solid..

Yield = 171mg (49%)

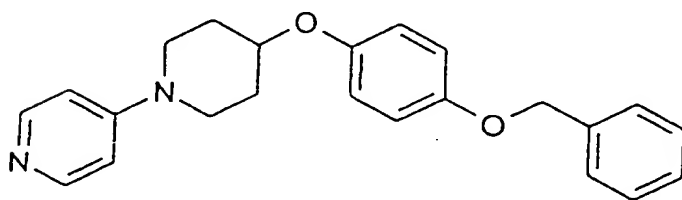
R_f = 0.28 (5%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): δ = 2.4 (m, 2H), 2.45 (s, 3H), 3.55 (m, 3H), 3.78 (dd, 1H), 5.84 (m, 1H), 6.25 (m, 2H), 6.8 (d, 1H), 8.12 (d, 1H), 8.36 (dd, 1H), 9.08 (d, 1H).

MS (ESP+): m/e 301 (M+H)⁺.

Example 951-(5-bromo-2-pyridyl)-4-(4-pyridyl)piperazine

A mixture of 1-(4-pyridyl)piperazine (3.26 g, 20mmol) and 2,5-dibromopyridine (2.36 g) was heated gradually on an oil bath up to 200°C. At approximately 150°C a clear, slightly
 10 coloured melt was obtained and at approximately 180°C a vigorous reaction set in which caused the melt to darken markedly. The now-dark melt was heated at 200°C for 10 minutes then allowed to cool to room temperature. The solid reaction mixture was dissolved in methanol (100 mL) and poured into water (100 - 150 mL). The resultant precipitate was collected, washed with water, dried, then recrystallised from hot aqueous methanol to give the
 15 product (1.6 g, 25% yield) as a buff-coloured solid: m.p. 176 - 180°C; NMR (DMSO-d₆), 3.32 (4H, m), 3.50 (4H, m), 6.72 (2H, m), 6.75 (1H, d), 7.59 (1H, dd), 8.05 (3H, m); Found: MH⁺, 319/321; C₁₄H₁₅BrN₄ requires MH⁺, 319/321.

Example 9620 1-(4-pyridyl)-4-((4-benzoyloxy)phenyloxy)piperidine

Scale: 5.0mmol

25

Method E, using hydroquinone monobenzyl ether and 1-(4-pyridyl)-4-hydroxypiperidine. The residue was purified by column chromatography, eluting sequentially with EtOAc; CH₂Cl₂; 5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂ giving an off-white solid.
Yield = 232mg (13%)

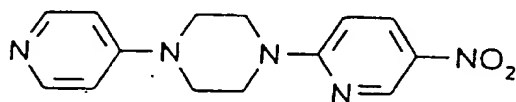
5 R_f = 0.25 (10%MeOH/CH₂Cl₂)

¹H-NMR (250MHz, CDCl₃): δ = 1.95 (m, 4H), 3.30 (m, 2H), 3.65 (m, 2H), 4.43 (m, 1H), 5.02 (s, 2H), 6.68 (m, 2H), 6.90 (m, 4H), 7.38 (m, 5H), 8.27 (d, 2H).

MS (ESP+): m/e 361 (M+H)⁺.

10 Example 97

1-(5-nitro-2-pyridyl)-4-(4-pyridyl)piperazine



15 Scale: 350mg, 2.15mmol

Method F, using 2-bromo-5-nitropyridine. The product was isolated by filtration of the reaction mixture, washed with water and dried azeotropically with toluene.

Yield = 490mg (80%) yellow powder

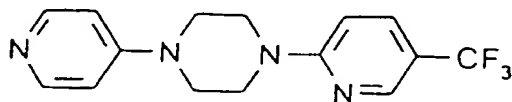
20 R_f = 0.15 (10%MeOH/CH₂Cl₂)

¹H-NMR (200MHz, DMSO-d₆): δ = 3.52 (m, 4H), 3.92 (m, 4H), 6.82 (m, 2H), 6.98 (d, 1H), 8.23 (m, 3H), 9.0 (d, 1H).

MS (CI+): m/e 286.6 (M+H)⁺.

25 Example 98

1-(5-trifluoromethyl-2-pyridyl)-4-(4-pyridyl)piperazine



Scale: 325mg, 2.0mmol

Method F, using 2-bromo-5-trifluoromethylpyridine. Purification by column chromatography on silica, eluting with CH_2Cl_2 and increasing gradually to 10%MeOH/ CH_2Cl_2 , gave the product as an off-white solid.

Yield = 150mg (24%) cream solid

R_f = 0.35 (10%MeOH/ CH_2Cl_2)

$^1\text{H-NMR}$ (250MHz, CDCl_3): δ = 3.5 (m, 4H), 3.82 (m, 4H), 6.66 (m, 3H), 7.66 (dd, 1H), 8.28 (m, 2H), 8.42 (m, 1H).

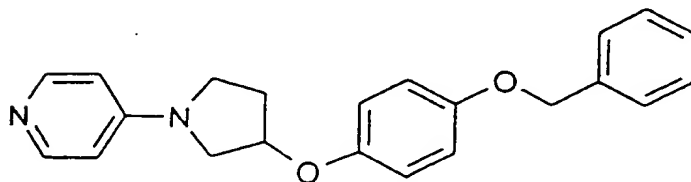
MS (CI+): m/e 309 (M+H) $^+$.

Found: C,58.4; H,4.9; N,17.9; $\text{C}_{15}\text{H}_{15}\text{F}_3\text{N}_4$ requires: C,58.4; H,4.90; N,18.2%.

Example 99

1-(4-pyridyl)-3-(4-benzyloxyphenoxy)pyrrolidine

15



Scale: 2.6 g, 8.52 mmol

20 Method A using 4-chloropyridine hydrochloride and 3-(4-benzyloxyphenoxy)pyrrolidine hydrochloride. The reaction mixture was taken to pH 8.5 using aqueous NaOH solution and the product was extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*, and the residue columned on silica, eluting with 10%MeOH/1% NH_4OH / CH_2Cl_2 , giving a yellow gum.

25 Yield = 1.55 g (53%)

R_f = 0.35 (10%MeOH/1% NH_4OH / CH_2Cl_2)

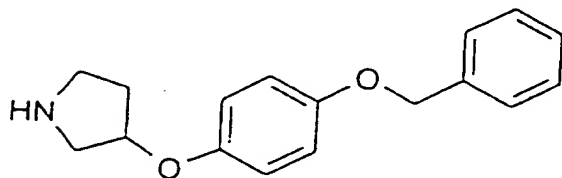
$^1\text{H-NMR}$ (200 MHz, d_6 -DMSO): δ = 2.24 (m, 2H), 3.40 (m, 3H), 3.64 (dd, 1H), 5.05 (s, 2H), 5.07 (m, 1H), 6.52 (d, 2H), 6.93 (m, 4H), 7.40 (m, 5H), 8.11 (d, 2H).

MS (ESP+): m/e 347 (M+H)⁺.

Found: C, 74.3; H, 6.4; N, 7.7; C₂₂H₂₂N₂O₂·0.5H₂O requires: C, 74.2; H, 6.2; N, 7.9%.

The precursor 3-(4-benzyloxyphenoxy)pyrrolidine hydrochloride was prepared in two steps
5 from hydroquinone monobenzyl ether as follows:

3-(4-benzyloxyphenoxy)pyrrolidine hydrochloride



10

Scale: 3.82 g, 19.1 mmol.

Method E using hydroquinone monobenzyl ether and 1-(tert-butyloxycarbonyl)-3-pyrrolidinol. The solvent was evaporated and the residue columned on silica, eluting
15 sequentially with CH₂Cl₂; 30% EtOAc/hexane giving a yellow oil. This was dissolved in EtOAc (200 ml) under Ar and a saturated solution of hydrogen chloride in Et₂O (100 ml) was added. The mixture was stirred for 4 h. The product was filtered off as a white solid.

Yield: 2.61 g (45%)

R_f = 0.24 (10% MeOH/1% NH₄OH/CH₂Cl₂)

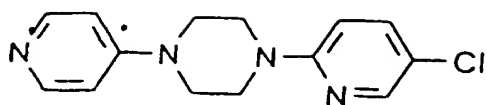
20 ¹H-NMR (250 MHz, d⁶-DMSO): δ = 2.12 (m, 2H), 3.27 (m, 3H), 3.41 (dd, 1H), 5.03 (m, 1H), 5.05 (s, 2H), 6.94 (m, 4H), 7.37 (m, 5H), 9.51 (br s, 1H)

MS (ESP+): m/e 270 (M+H)⁺.

Found: C, 66.5; H, 6.6; N, 4.6; C₁₇H₂₀ClNO₂ requires: C, 66.8; H, 6.6; N, 4.6%.

25 Example 100

1-(5-chloro-2-pyridyl)-4-(4-pyridyl)piperazine



Scale: 312mg, 1.91mmol

5 Method F, using 2,5-dichloropyridine. The residue was purified by column chromatography on silica, eluting with CH_2Cl_2 , then 5%MeOH/ CH_2Cl_2 .

Yield = 30mg (6%) light brown solid

R_f = 0.3 (10%MeOH/ CH_2Cl_2)

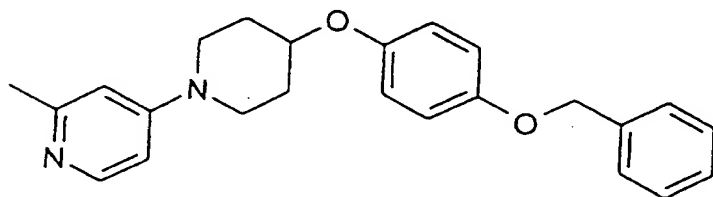
$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 3.43 (m, 4H), 3.64 (m, 4H), 6.6 (d, 1H), 6.7 (d, 2H), 7.23
10 (dd, 1H), 8.15 (m, 1H), 8.32 (d, 2H).

MS (ESP+): m/e 275/7 ($\text{M}+\text{H}$) $^+$.

Example 101

1-(4-(2-methyl)pyridyl)-4-((4-benzyloxy)phenyloxy)piperidine

15



Scale: 1.3mmol

20 (4-Benzyloxy)phenyloxy)piperidine (1 eq) (made from 1-t-butyloxycarbonyl-4-hydroxypiperidine by Mitsunobu reaction with hydroquinone monobenzyl ether followed by treatment with trifluoroacetic acid) and 2-methyl-4-chloropyridine (2 eq) were heated in t-butanol (2.5 ml) and aqueous HCl (2M; 0.1ml) at reflux overnight. The solvents were evaporated and the residue partitioned between CH_2Cl_2 and 10% aqueous potassium carbonate
25 solution. The organic layer was washed with water and brine, dried over sodium sulphate and concentrated. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving an off-white powder.

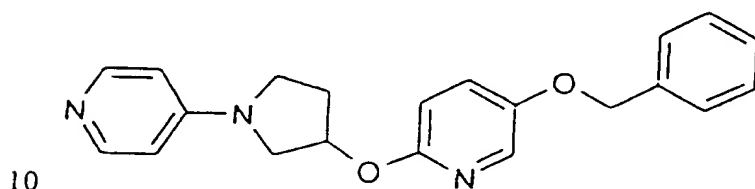
Yield = 70mg (14%)

$R_f = 0.44$ (10%MeOH/ CH_2Cl_2)

$^1\text{H-NMR}$ (250MHz, CDCl_3): $\delta = 2.0$ (m, 4H), 2.62 (s, 3H), 3.58 (m, 2H), 3.70 (m, 2H), 4.52 (m, 1H), 5.02 (s, 2H), 6.58 (m, 1H), 6.68 (dd, 1H), 6.88 (m, 4H), 7.38 (m, 5H), 8.08 (d, 2H).
 5 MS (ESP+): m/e 375 ($\text{M}+\text{H}$) $^+$.

Example 102

1-(4-pyridyl)-3-(5-benzoyloxy-2-pyridyloxy)pyrrolidine



Scale: 6.02 g, 27.4 mmol

Method B, using using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloro-5-benzoyloxy pyridine,
 15 heating to 120°C for 3 h. After cooling the t-butanol was removed on a rotary evaporator.

The dark residue was dissolved in CH_2Cl_2 and the solution washed with 10% aqueous NaOH solution before concentration *in vacuo*. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; Et_2O ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving a brown oil.

Yield = 5.70 g (66%)

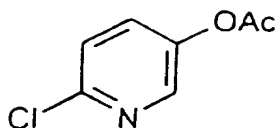
20 $R_f = 0.38$ (10%MeOH/1% NH_4OH / CH_2Cl_2)

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 2.33$ (m, 2H), 3.5 (m, 3H), 3.71 (dd, 1H), 5.04 (s, 2H), 5.63 (m, 1H), 6.40 (d, 2H), 6.64 (d, 1H), 7.26 (dd, 1H), 7.3 (m, 5H), 7.88 (d, 1H), 8.21 (d, 2H).

MS (ESP+): m/e 348 ($\text{M}+\text{H}$) $^+$.

25 The precursor 2-chloro-5-benzoyloxy pyridine was prepared in three steps from 5-amino-2-chloropyridine as follows:

2-chloro-5-acetoxypyridine



Scale: 25.9 g, 201 mmol

5

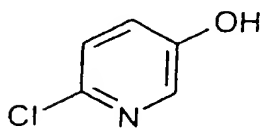
Method: a solution of 5-amino-2-chloropyridine (25.9 g, 201 mmol) in ethanol (185 ml) was cooled in an ice-methanol bath. 50% aqueous tetrafluoroboric acid (78 ml, 442 mmol) was added. When the internal temperature reached -5°C isoamyl nitrite (28.4 ml, 211 mmol) was added dropwise keeping the temperature below 0°C. After addition the reaction mixture was stirred at 0°C for 30 minutes. An orange solid appeared which was collected on a Buchner funnel, washed with Et₂O and dried on the Buchner funnel for 15 minutes. The solid was dissolved in acetic anhydride (240 ml) and the resulting solution warmed slowly to 70°C. Heating was continued for 4 hours during which time N₂ gas was evolved. The mixture was allowed to cool then concentrated *in vacuo*. The residue was dissolved in Et₂O (300 ml) and washed three times with water, then with brine, dried (Na₂SO₄) and concentrated *in vacuo* giving a red-brown oil. The product was purified by Kugelrohr distillation (oven temperature 110°C, 1.6 mbar) giving a white solid.

Yield = 16.5 g (48%)

R_f = 0.74 (10% Et₂O/CH₂Cl₂)

20 ¹H-NMR (300 MHz, CDCl₃): δ = 2.33 (s, 3H), 7.34 (d, 1H), 7.47 (dd, 1H), 8.21 (d, 1H).

2-chloro-5-hydroxypyridine



25

Scale: 16.5 g, 96.2 mmol

Method: 2-chloro-5-acetoxypyridine (16.5 g, 96.2 mmol) was dissolved in 2M aqueous KOH solution (125 ml) with ice-bath cooling. The resulting solution was stirred at 4°C for 3 hours after which time the reaction was judged complete by tlc. The reaction mixture was neutralised by the addition of acetic acid (approx. 10 ml) whereupon a white solid appeared.

5 The product was collected on a Buchner funnel and dried under high vacuum at 40°C.

Yield = 11.9 g (96%)

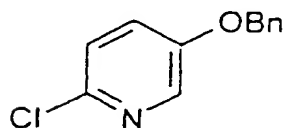
$R_f = 0.21$ (10%Et₂O/CH₂Cl₂)

¹H-NMR (300 MHz, d⁶-DMSO): δ = 7.2 (m, 2H), 7.87 (d, 1H).

MS (ESP+): m/e 130/2 (M+H)⁺.

10 Found: C,46.3; H,3.1; N,10.7; C₅H₄ClNO requires: C,46.4; H,3.11; N,10.8%.

2-chloro-5-benzoyloxy pyridine



15

Scale: 6.05 g, 46.7 mmol

Method: under argon, 2-chloro-5-hydroxypyridine (6.05 g, 46.7 mmol) was dissolved in anhydrous DMF (50 ml) and the resulting solution cooled in an ice-water bath. Sodium methoxide (2.78 g, 51.4 mmol) was added and the mixture stirred for 10 minutes. Benzyl bromide (8.79 g, 51.4 mmol) was added and the resulting mixture stirred for 90 minutes with gradual warming to room temperature. The mixture was poured into ice-water (600 ml). The mixture was extracted thrice with Et₂O and the combined extracts washed with water and brine, dried (MgSO₄) and concentrated *in vacuo* giving a clear yellow oil. The product was

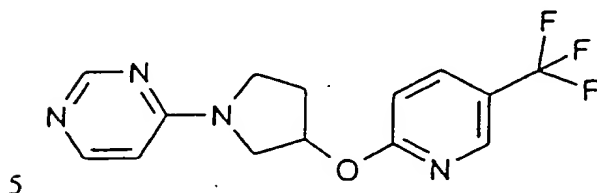
25 purified by column chromatography, eluting sequentially with 10%Et₂O/isohexane;25% Et₂O/isohexane yielding a white solid.

Yield = 8.18 g (80%)

$R_f = 0.36$ (CH₂Cl₂)

¹H-NMR (300 MHz, CDCl₃): δ = 5.09 (s, 2H), 7.27 (d, 1H), 7.35 (m, 6H), 8.14 (d, 1H).

30 MS (ESP-): m/e 220/2 (M-H)⁻.

Example 1031-(4-pyrimidinyl)-3-(5-(trifluoromethyl)-2-pyridyloxy)pyrrolidine

Scale: 1.7mmol

Method A in 10% aqueous isopropanol, using 4-chloropyrimidine and 3-(5-(trifluoromethyl)-2-pyridyloxy)pyrrolidine. After evaporation of the solvents, the residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$ giving an off-white solid.

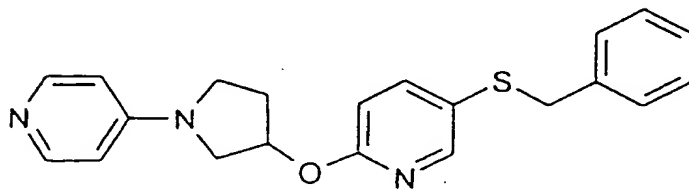
Yield = 379mg (72%)

$R_f = 0.53$ (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

15 $^1\text{H-NMR}$ (200MHz, CDCl_3): $\delta = 2.38$ (m, 2H), 3.75 (m, 4H), 5.78 (m, 1H), 6.30 (d, 1H), 6.80 (d, 1H), 7.80 (d, 1H), 8.18 (d, 1H), 8.42 (s, 1H), 8.60 (s, 1H).

MS (ESP+): m/e 311 ($\text{M}+\text{H}$) $^+$.

Found: C,53.8; H,4.2; N,17.6; $\text{C}_{14}\text{H}_{13}\text{F}_3\text{N}_4\text{O}$ requires: C54.2; H,4.22; N,18.1%.

20 Example 1041-(4-pyridyl)-3-(5-benzylthio-2-pyridyloxy)pyrrolidine

25 Scale: 524 mg, 3.19 mmol

Method B, 0.5 M in anhydrous THF and without tetra-n-butylammonium bromide, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloro-5-benzylthio-pyridine. The product was purified by column chromatography, eluting sequentially with Et₂O; 5%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving a pale yellow gum.

5 Yield = 517 mg (45%)

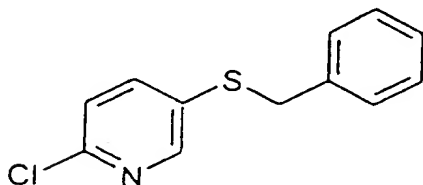
R_f = 0.33 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300 MHz, CDCl₃): d = 2.35 (m, 2H), 3.5 (m, 3H), 3.72 (dd, 1H), 3.96 (s, 2H), 5.66 (m, 1H), 6.41 (d, 2H), 6.59 (d, 1H), 7.17 (m, 2H), 7.24 (m, 3H), 7.45 (dd, 1H), 8.07 (d, 1H), 8.10 (d, 2H).

10 MS (ESP+): m/e 364 (M+H)⁺.

The precursor 2-chloro-5-benzylthiopyridine was prepared in two steps from 5-amino-2-chloropyridine as follows:

15 2-chloro-5-benzylthiopyridine



Scale: 628 mg, 3.68 mmol

20 Method: 2-chloro-5-thiocyanopyridine (628 mg, 3.68 mmol) and benzyl bromide (692 mg, 4.05 mmol) were dissolved in THF (6 ml) and a solution of potassium hydroxide (512 mg, 9.13 mmol) in water (5 ml) was added. The resulting mixture was heated to 100°C for 2 hours. The mixture was allowed to cool then extracted with Et₂O (3 x 10 ml). The combined extracts were dried (MgSO₄) and concentrated *in vacuo*, yielding a yellow oil.

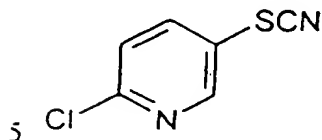
25 Yield = 828 mg (95%)

R_f = 0.45 (CH₂Cl₂)

¹H-NMR (250 MHz, CDCl₃): d = 4.06 (s, 2H), 7.18 (d, 1H), 7.25 (m, 5H), 7.48 (dd, 1H), 8.26 (d, 1H).

MS (ESP+): m/e 236/8 (M+H)⁺.

2-chloro-5-thiocyanopyridine



Scale: 5.42 g, 42.1 mmol

Method: 5-amino-2-chloropyridine (5.42 g, 42.1 mmol) was dissolved in concentrated aqueous hydrochloric acid (75 ml) and the resulting solution cooled in an ice-methanol bath. A solution of sodium nitrite (3.58 g, 42.2 mmol) in water (15 ml) was added slowly, keeping the internal reaction temperature below 0°C. After addition the reaction mixture was stirred at 0°C for 30 minutes then added portionwise to a stirred solution of copper (I) thiocyanate (2.8 g, 23 mmol) and potassium thiocyanate (25 g) in water (525 ml). After addition the mixture stirred for 15 minutes at room temperature. The mixture was filtered through a celite pad, and the pad washed thoroughly with Et₂O. The layers were separated and the aqueous layer extracted with Et₂O (3 x 100 ml). The combined organic phases were washed with water, brine and saturated aqueous NaHCO₃ solution, dried (MgSO₄) and concentrated *in vacuo*, yielding a yellow oil which solidified on standing. The crude product was purified by Kügelrohr distillation (oven temperature 125°C, 2.4 mbar) yielding a white solid.

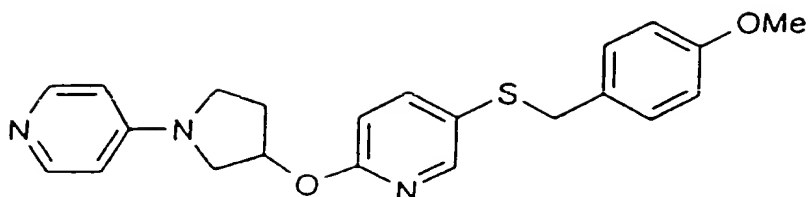
Yield = 2.55 g (35%)

¹H-NMR (300 MHz, CDCl₃): δ = 7.44 (d, 1H), 7.88 (dd, 1H), 8.54 (d, 1H).

MS (CI-): m/e 171/3 (M+H)⁺.

25 Example 105

1-(4-pyridyl)-3-(5-(4-methoxybenzyl)thio-2-pyridyl)oxy)pyrrolidine



Scale: 88 mg, 0.33 mmol

Method B, 0.5 M in anhydrous THF and without tetra-n-butylammonium bromide, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloro-5-(4-methoxybenzyl)thio-pyridine. The product was purified by column chromatography, eluting sequentially with Et₂O; 5%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving a pale yellow gum.

Yield = 102 mg (78%)

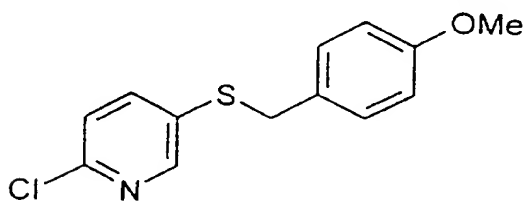
R_f = 0.30 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300 MHz, CDCl₃): δ = 2.36 (m, 2H), 3.52 (m, 3H), 3.74 (dd, 1H), 3.78 (s, 3H), 3.90 (s, 2H), 5.67 (m, 1H), 6.44 (d, 2H), 6.58 (d, 1H), 6.79 (d, 2H), 7.07 (d, 2H), 7.45 (dd, 1H), 8.06 (d, 1H), 8.20 (d, 2H).

MS (ESP+): m/e 394 (M+H)⁺.

15 The precursor 2-chloro-5-(4-methoxybenzyl)thiopyridine was prepared in two steps from 5-amino-2-chloropyridine as follows:

2-chloro-5-(4-methoxybenzyl)thiopyridine



20

Scale: 98 mg, 0.574 mmol

Method: 2-chloro-5-thiocyanopyridine (98 mg, 0.574 mmol) and benzyl bromide (90 mg, 0.574 mmol) were dissolved in THF (2.5 ml) and a solution of potassium hydroxide (80 mg, 1.44 mmol) in water (2.5 ml) was added. The resulting mixture was heated to 85°C for 1.5

25

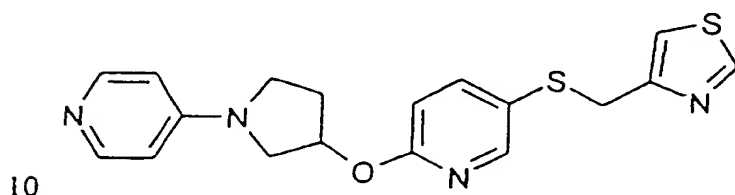
hours. The mixture was allowed to cool then extracted with Et₂O (3 x 10 ml). The combined extracts were dried (MgSO₄) and concentrated *in vacuo*, yielding a yellow oil.

Yield = 92.5 mg (63%)

R_f = 0.45 (CH₂Cl₂)

¹H-NMR (300 MHz, CDCl₃): δ = 3.78 (s, 3H), 4.03 (s, 2H), 6.81 (d, 2H), 7.15 (d, 2H), 7.19 (d, 1H), 7.48 (dd, 1H), 8.26 (d, 1H).

1-(4-pyridyl)-3-(5-(4-thiazolyl)methylthio-2-pyridyloxy)pyrrolidine



Scale: 125 mg, 0.515 mmol

Method B, 0.5 M in anhydrous THF and without tetra-*n*-butylammonium bromide, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloro-5-(4-thiazolyl)methylthiopyridine. The product was purified by column chromatography, eluting sequentially with Et₂O; 10% MeOH/1% NH₄OH/CH₂Cl₂ giving a pale yellow gum.

Yield = 125 mg (66%)

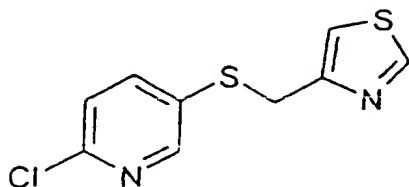
R_f = 0.30 (10% MeOH/1% NH₄OH/CH₂Cl₂)

¹H-NMR (300 MHz, CDCl₃): δ = 2.35 (m, 2H), 3.5 (m, 3H), 3.63 (dd, 1H), 4.16 (s, 2H), 5.68 (m, 1H), 6.42 (d, 2H), 6.61 (d, 1H), 6.97 (s, 1H), 7.53 (dd, 1H), 8.11 (d, 1H), 8.20 (d, 2H), 8.78 (s, 1H).

MS (ESP+): m/e 371 (M+H)⁺

The precursor 2-chloro-5-(4-thiazolyl)methylthiopyridine was prepared in one step from 2-chloro-5-thiocyanopyridine as follows:

2-chloro-5-(4-thiazolyl)methylthiopyridine



Scale: 96.5 mg, 0.566 mmol

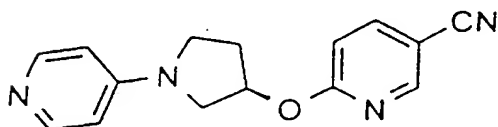
5 Method: 2-chloro-5-thiocyanopyridine (96.5 mg, 0.566 mmol), 4-chloromethylthiazole hydrochloride (96.2 mg, 0.566 mmol) and potassium hydroxide (79.3 mg, 1.41 mmol) were suspended in 1:1 THF/water (5 ml). The resulting mixture was heated to 85°C for 90 minutes and allowed to cool. The mixture was extracted with Et₂O (3 x 10 ml) and the combined extracts were dried (MgSO₄) and concentrated *in vacuo* giving a colourless oil which was
10 used directly in the next step.

Yield = 125 mg (91%)

Examples 106/107

(3R)-1-(4-pyridyl)-3-(5-cyano-2-pyridyloxy)pyrrolidine

15



Scale: 492mg, 3.0mmol

20 Method B (without tetrabutylammonium bromide) in THF (0.6M), using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloro-5-cyanopyridine, with 5hr reaction time. After evaporation of the solvent, the residue was purified by column chromatography, eluting sequentially with CH₂Cl₂; 5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving an off-white solid.

25 Yield = 255mg (32%)

R_f = 0.36 (10%MeOH/1%NH₄OH/CH₂Cl₂)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.4 (m, 2H), 3.58 (m, 3H), 3.78 (dd, 1H), 5.80 (m, 1H), 6.42 (d, 2H), 6.80 (d, 1H), 7.80 (dd, 1H), 8.22 (d, 2H), 8.50 (s, 1H).

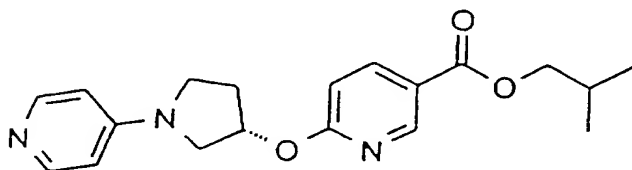
MS (ESP+): m/e 267 ($\text{M}+\text{H}$) $^+$.

- 5 The (S) enantiomer was also prepared by the same method in 30% yield from the (S) alcohol, and gave identical analytical data.

Examples 108/109

(3S)-1-(4-pyridyl)-3-(5-isobutyloxycarbonyl-2-pyridyloxy)pyrrolidine

10



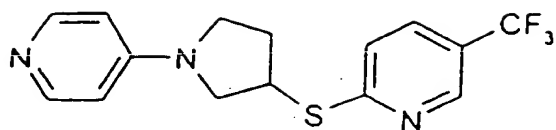
Scale: 0.78mmol

- 15 Method D, using (S)-1-(4-pyridyl)-3-hydroxypyrrolidine and isobutyl 2-chloronicotinate. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving a brown oil. Yield = 178mg (67%)
 R_f = 0.36 (10%MeOH/1% NH_4OH / CH_2Cl_2)
- 20 $^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 1.02 (d, 6H), 2.05 (m, 1H), 2.38 (m, 2H), 3.55 (m, 3H), 3.76 (dd, 1H), 4.10 (d, 2H), 5.80 (m, 1H), 6.41 (m, 2H), 6.75 (d, 1H), 8.20 (m, 3H), 8.83 (d, 1H).
 MS (ESP+): m/e 342 ($\text{M}+\text{H}$) $^+$.

The (R) enantiomer was also prepared by the same method in 30% yield from the (S) alcohol,
 25 and gave identical analytical data.

Example 110

1-(4-pyridyl)-3-(5-trifluoromethyl-2-pyridylthio)pyrrolidine



Scale: 250 mg, 1.52 mmol

5

Method E, using 1-(4-pyridyl)-3-hydroxypyrrolidine and 2-mercapto-5-trifluoromethylpyridine. The solvent was evaporated and the residue columned on silica, eluting sequentially with CH_2Cl_2 ; Et_2O ; 10% MeOH/1% NH_4OH / CH_2Cl_2 , giving a brown oil. Yield = 201 mg (40%)

10 $R_f = 0.30$ (10% MeOH/1% NH_4OH / CH_2Cl_2)

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ = 2.20 (m, 1H), 2.60 (m, 1H), 3.39 (dd, 1H), 3.52 (m, 2H), 3.98 (dd, 1H), 4.59 (m, 1H), 6.40 (d, 2H), 7.27 (d, 1H), 7.66 (d, 1H), 8.22 (d, 2H), 8.69 (s, 1H).

$^{13}\text{C-NMR}$ (400 MHz, CDCl_3): δ = 31.2, 41.3, 46.1, 53.4, 107.0, 121.8, 132.7, 146.3, 148.6,

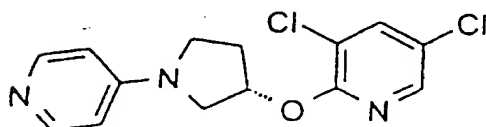
15 151.7, 163.2. 3 quaternaries missing

MS (ESP+): m/e 326 ($\text{M}+\text{H}$) $^+$.

Example 111

(S)-1-(4-pyridyl)-3-(3,5-dichloro-2-pyridyloxy)pyrrolidine

20



Scale: 0.91 mmol

25 Method D in THF without n-butylammonium bromide, using (S)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,3,5-trichloropyridine. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5% MeOH/ CH_2Cl_2 ; 10% MeOH/ CH_2Cl_2 ; 10% MeOH/1% NH_4OH / CH_2Cl_2 giving a brown oil.

Yield = 283mg (quantitative)

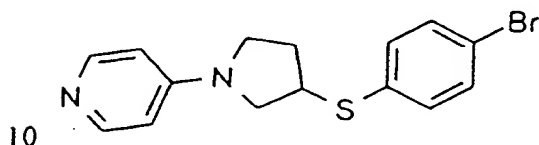
$R_f = 0.22$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): $\delta = 2.38$ (m, 2H), 3.55 (m, 3H), 3.78 (dd, 1H), 5.68 (m, 1H), 6.41 (d, 2H), 7.63 (m, 1H), 8.02 (s, 1H), 8.22 (d, 2H).

5 MS (ESP+): m/e 310 (M+H)⁺.

Example 112

1-(4-pyridyl)-3-(4-(bromo)phenylthio)pyrrolidine



Scale: 0.84mmol

Method G, using 4-bromothiophenol. The residue was purified by column chromatography,
15 eluting sequentially with CH₂Cl₂; 5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂ giving a colourless solid.

Yield = 175mg (62%)

$R_f = 0.32$ (10%MeOH/CH₂Cl₂)

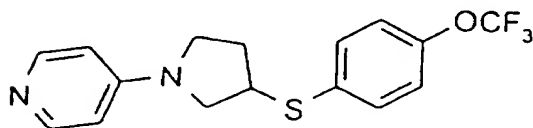
¹H-NMR (300MHz, CDCl₃): $\delta = 2.08$ (m, 1H), 2.40 (m, 1H), 3.30 (m, 1H), 3.39 (m, 1H), 3.52
20 (m, 1H), 3.68 (m, 1H), 3.90 (m, 1H), 6.36 (d, 2H), 7.28 (d, 2H), 7.44 (d, 2H), 8.22 (d, 2H).

MS (ESP+): m/e 335/337 (M+H)⁺.

Example 113

1-(4-pyridyl)-3-(4-(trifluoromethoxy)phenylthio)pyrrolidine

25



Scale: 0.84mmol

Method G, using 4-(trifluoromethoxy)thiophenol. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 , giving an off-white solid.

5 Yield = 165mg (58%)

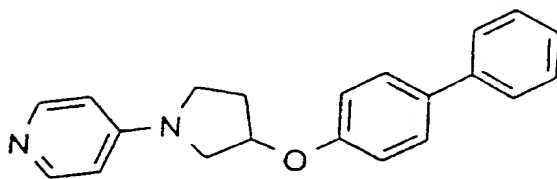
R_f = 0.32 (10%MeOH/ CH_2Cl_2)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.10 (m, 1H), 2.42 (m, 1H), 3.32 (m, 1H), 3.41 (m, 1H), 3.54 (m, 1H), 3.72 (m, 1H), 3.92 (m, 1H), 6.35 (d, 2H), 7.18 (d, 2H), 7.45 (d, 2H), 8.22 (d, 2H);
MS (ESP+): m/e 341 (M+H) $^+$.

10

Example 114

1-(4-pyridyl)-3-((4-phenyl)phenoxy)pyrrolidine



15

Scale: 1.83mmol

Method E, using 4-phenylphenol. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ;

20 10%MeOH/1% NH_4OH / CH_2Cl_2 giving a white solid.

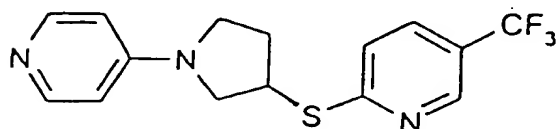
Yield = 169mg (29%)

R_f = 0.40 (10%MeOH/1% NH_4OH / CH_2Cl_2)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.35 (m, 1H), 2.55 (m, 3H), 3.58 (m, 3H), 3.76 (dd, 1H), 5.15 (m, 1H), 6.43 (m, 2H), 6.98 (d, 2H), 7.32 (dd, 1H), 7.42 (t, 2H), 7.55 (m, 4H), 8.21 (d, 2H).

MS (ESP+): m/e 317 (M+H) $^+$.

Example 115

(R)-1-(4-pyridyl)-3-(5-trifluoromethyl-2-pyridylthio)pyrrolidine

5 Scale: 400 mg, 2.43 mmol

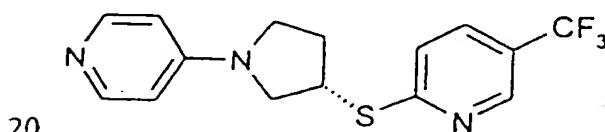
Method E. using (S)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-mercapto-5-trifluoromethylpyridine. The solvent was evaporated and the residue columned on silica, eluting sequentially with CH_2Cl_2 ; Et_2O ; 10%MeOH/1% NH_4OH / CH_2Cl_2 , giving a brown oil.

10 Yield = 681 mg (86%)

$R_f = 0.30$ (10%MeOH/1% NH_4OH / CH_2Cl_2)

^1H -NMR (300 MHz, CDCl_3): δ = 2.20 (m, 1H), 2.60 (m, 1H), 3.39 (dd, 1H), 3.52 (m, 2H), 3.98 (dd, 1H), 4.59 (m, 1H), 6.40 (d, 2H), 7.27 (d, 1H), 7.66 (d, 1H), 8.22 (d, 2H), 8.69 (s, 1H).

15 MS (ESP+): m/e 326 ($\text{M}+\text{H}$) $^+$.

Example 116(S)-1-(4-pyridyl)-3-(5-trifluoromethyl-2-pyridylthio)pyrrolidine

20

Scale: 400 mg, 2.43 mmol

Method E. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-mercapto-5-trifluoromethylpyridine. The solvent was evaporated and the residue columned on silica, eluting sequentially with CH_2Cl_2 ; Et_2O ; 10%MeOH/1% NH_4OH / CH_2Cl_2 , giving a brown oil.

25 Yield = 663 mg (83%)

$R_f = 0.30$ (10%MeOH/1% NH_4OH / CH_2Cl_2)

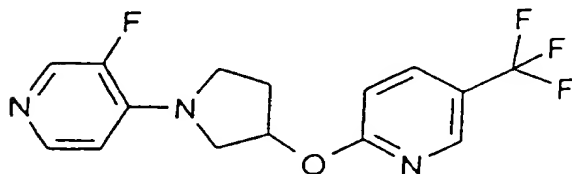
¹H-NMR (300 MHz, CDCl₃): δ = 2.20 (m, 1H), 2.60 (m, 1H), 3.39 (dd, 1H), 3.52 (m, 2H), 3.98 (dd, 1H), 4.59 (m, 1H), 6.40 (d, 2H), 7.27 (d, 1H), 7.66 (d, 1H), 8.22 (d, 2H), 8.69 (s, 1H).

MS (ESP+): m/e 326 (M+H)⁺.

5

Example 117

1-(3-fluoro-4-pyridyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



10

Scale: 1.5mmol

Method E. using 1-(3-fluoro-4-pyridyl)-3-hydroxypyrrolidine and 2-hydroxy-5-trifluoromethylpyridine. The product was isolated as a pale yellow gum.

15 Yield = 105mg (22%)

R_f = 0.20 (EtOAc)

¹H-NMR (200MHz, CDCl₃): δ = 2.30 (m, 2H), 3.70 (m, 3H), 3.95 (m, 1H), 5.76 (m, 1H), 6.22 (m, 1H), 6.80 (d, 1H), 7.78 (dd, 1H), 8.04 (d, 1H), 8.12 (d, 1H), 8.42 (s, 1H).

MS (ESP+): m/e 328 (M+H)⁺.

20

1-(3-Fluoro-4-pyridyl)-3-hydroxypyrrolidine was generated in four steps from 1-(4-pyridyl)-3-hydroxypyrrolidine as follows:

1-(4-Pyridyl)-3-(t-butyl(dimethylsilyloxy)pyrrolidine

25

1-(4-Pyridyl)-3-hydroxypyrrolidine (5.02g, 30.6mmol) was dissolved in DMF (40ml) and imidazole (9.18g, 135mmol) was added, followed by a solution of t-butylchlorodimethylsilane (10.20g, 67.7mmol) in DMF (25ml). After stirring overnight the mixture was partitioned between water and dichloromethane. The organic layer was dried over sodium sulphate.

After evaporation of the solvents, the residue was purified by column chromatography on alumina, eluting sequentially with CH_2Cl_2 ; EtOAc; 10%MeOH/EtOAc; 50%MeOH/EtOAc giving a clear yellow oil.

Yield = quantitative

5 $R_f = 0.38$ (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (200MHz, CDCl_3): $\delta = 0.01$ (d, 6H), 0.80 (s, 9H), 1.95 (m, 2H), 3.07 (dd, 1H), 3.25 (m, 1H), 3.38 (m, 2H), 4.44 (m, 1H), 6.24 (d, 2H), 8.11 (d, 2H).

1-(3-Bromo-4-pyridyl)-3-(t-butyl dimethylsilyloxy)pyrrolidine

10

1-(4-Pyridyl)-3-(t-butyl dimethylsilyloxy)pyrrolidine (8.92g, 32.1mmol) was dissolved in acetonitrile (140ml) and N-bromosuccinimide (6.00g, 33.7mmol) was added portionwise. After stirring overnight the solvent was removed under reduced pressure and the residue partitioned between dichloromethane and water. The organic layer was dried over sodium

15 sulphate. After evaporation of the solvent, the residue was purified by column

chromatography on silica gel, eluting sequentially with CH_2Cl_2 ; 5%MeOH CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 . Further purification by column chromatography on alumina, eluting sequentially with isohexane; 25%EtOAc/isohexane gave the product as a colourless oil.

Yield = 3.44g (30%)

20 $R_f = 0.70$ (10%MeOH/1% $\text{NH}_4\text{OH}/\text{CH}_2\text{Cl}_2$)

$^1\text{H-NMR}$ (200MHz, CDCl_3): $\delta = 0.0$ (d, 6H), 0.80 (s, 9H), 1.90 (m, 2H), 3.38 (dd, 1H), 3.48 (m, 1H), 3.62 (m, 1H), 3.80 (dd, 1H), 4.40 (m, 1H), 6.40 (d, 1H), 8.02 (d, 1H), 8.30 (s, 1H). MS (ESP+): m/e 357/359 (M+H) $^+$.

25 1-(3-Fluoro-4-pyridyl)-3-(t-butyl dimethylsilyloxy)pyrrolidine

A solution of 1-(3-bromo-4-pyridyl)-3-(t-butyl dimethylsilyloxy)pyrrolidine (1.07g, 3.0mmol) in THF (10ml) was added to a solution of t-butyl lithium (1.5M in hexanes, 4.2ml) in THF (10ml) at -78°C . After ten minutes a solution of N-fluorobisbenzenesulphonide (1.42g, 4.5mmol) in THF (10ml) was added dropwise. After a further hour at -78°C the mixture was

30 allowed to warm to room temperature. After stirring overnight the mixture was partitioned between dichloromethane and water. The organic layer was dried over sodium sulphate.

After evaporation of the solvent, the residue was purified by column chromatography on alumina, eluting sequentially with isohexane; 25%EtOAc/isohexane; 60%EtOAc/isohexane giving a pale yellow solid.

Yield = 0.47g (53%)

5 $R_f = 0.39$ (7%MeOH/ CH_2Cl_2)

$^1\text{H-NMR}$ (200MHz, CDCl_3): $\delta = 0.0$ (d, 6H), 0.80 (s, 9H), 1.90 (m, 2H), 3.26 (dm, 1H), 3.55 (m, 3H), 4.41 (m, 1H), 6.34 (m, 1H), 7.92 (d, 1H), 8.02 (d, 1H).

MS (ESP+): m/e 297 ($\text{M}+\text{H}$) $^+$.

10 1-(3-Fluoro-4-pyridyl)-3-hydroxypyrrolidine

1-(3-Fluoro-4-pyridyl)-3-(*t*-butyldimethylsilyloxy)pyrrolidine (0.45g, 1.52mmol) was dissolved in acetonitrile (10ml) and 1M HCl (aq) (2ml) was added. After stirring overnight solid potassium carbonate was added to render the solution alkaline. After standing at -15°C

15 for several days the white solid formed was isolated by filtration through a pad of alumina.

The pad was washed well with a mixture of methanol and dichloromethane and product-containing fractions were concentrated under vacuum to give a white solid.

Yield = 0.28g (ca. quantitative)

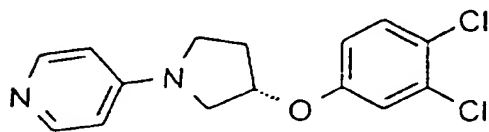
$R_f = 0.1$ (10%MeOH/ CH_2Cl_2)

20 $^1\text{H-NMR}$ (200MHz, d_6 -DMSO): $\delta = 1.90$ (m, 2H), 3.30 (dm, 1H), 3.55 (m, 3H), 4.35 (m, 1H), 6.58 (m, 1H), 7.94 (d, 1H), 8.06 (d, 1H).

MS (ESP+): m/e 183 ($\text{M}+\text{H}$) $^+$.

Examples 118/119

25 (S)-1-(4-pyridyl)-3-(3,4-dichlorophenoxy)pyrrolidine



Scale: 0.94mmol

Method G, using 3-methyl-4-(methylthio)phenol. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 .

Yield = 164mg (56%)

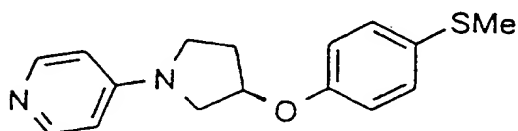
$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.30 (m, 2H), 3.52 (m, 3H), 3.65 (m, 1H), 5.02 (m, 1H), 6.40 (d, 2H), 6.74 (dd, 1H), 6.98 (m, 1H), 7.35 (d, 1H), 8.22 (d, 2H).

MS (ESP+): m/e 309/311/313 ($\text{M}+\text{H}$) $^+$.

The (R) enantiomer was also prepared by the same method, and gave identical analytical data.

10 Examples 120/121

1-(4-pyridyl)-3-(4-(methylthio)phenoxy)pyrrolidine



15 Scale: 0.94mmol

Method G, using 4-(methylthio)phenol. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 .

20 Yield = 131mg (49%)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.15 (m, 1H), 2.38 (m, 1H), 3.52 (m, 3H), 3.65 (m, 1H), 5.05 (m, 1H), 6.42 (d, 2H), 6.82 (d, 2H), 7.28 (d, 2H), 8.22 (d, 2H).

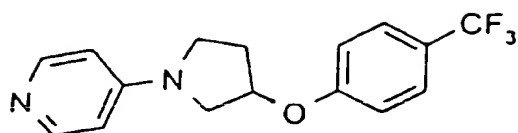
MS (ESP+): m/e 287 ($\text{M}+\text{H}$) $^+$.

The (S) enantiomer was also prepared by the same method, and gave identical analytical data.

25

Examples 122/123

1-(4-pyridyl)-3-(4-(trifluoromethyl)phenoxy)pyrrolidine



Scale: 0.94mmol

5 Method G, using 4-trifluoromethylphenol. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 .

Yield = 124mg (43%)

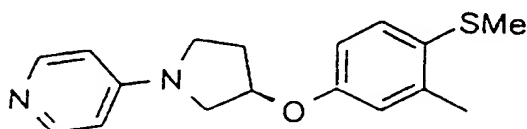
^1H -NMR (300MHz, CDCl_3): δ = 2.35 (m, 2H), 3.54 (m, 2H), 3.72 (m, 1H), 5.12 (m, 1H), 6.40 (d, 2H), 6.95 (d, 2H), 7.66 (d, 2H), 8.22 (d, 2H).

MS (ESP+): m/e 309 ($\text{M}+\text{H}$) $^+$.

The (S) enantiomer was also prepared by the same method, and gave identical analytical data.

Examples 124/125

15 (R)-1-(4-pyridyl)-3-(3-methyl-4-(methylthio)phenoxy)pyrrolidine



Scale: 0.94mmol

20

Method G, using 3-methyl-4-(methylthio)phenol. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 .

Yield = 77mg (27%)

25 ^1H -NMR (300MHz, CDCl_3): δ = 2.25 (m, 2H), 2.36 (s, 3H), 2.42 (s, 3H), 3.54 (m, 3H), 3.72 (m, 1H), 5.04 (m, 1H), 6.40 (d, 2H), 6.70 (m, 2H), 7.18 (m, 1H), 8.22 (d, 2H).

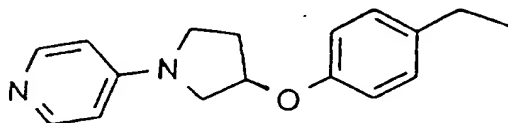
MS (ESP+): m/e 301 ($\text{M}+\text{H}$) $^+$.

The (S) enantiomer was also prepared by the same method, and gave identical analytical data.

Example 126

(3R)-1-(4-pyridyl)-3-(4-ethylphenoxy)pyrrolidine

5



Scale: 0.94mmol

10 Method G. using (S)-1-(4-pyridyl)-3-(p-toluenesulphonyloxy)pyrrolidine and 4-ethylphenol.

The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving a light brown solid.

Yield = 132mg (53%)

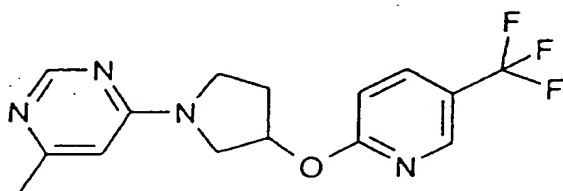
15 R_f = 0.4 (10%MeOH/1% NH_4OH / CH_2Cl_2)

$^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 1.22 (t, 3H), 2.25 (m, 1H), 2.38 (m, 1H), 2.60 (q, 2H), 3.55 (m, 3H), 3.65 (dd, 1H), 5.04 (m, 1H), 6.40 (m, 2H), 6.80 (d, 2H), 7.14 (d, 2H), 8.21 (d, 2H).

MS (ESP+): m/e 269 ($\text{M}+\text{H}$) $^+$.

20 Example 127

1-(6-methyl-4-pyrimidyl)-3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine



25 Scale: 1.5mmol

6-Methyl-4-chloropyrimidine (0.46mmol) (for preparation, see *Chem. Pharm. Bull.*, (1976), 24, 303) and 3-(5-trifluoromethyl-2-pyridyloxy)pyrrolidine (348mg, 1.5mmol) were heated with sodium bicarbonate (330mg, 3.9mmol) in ethanol (8ml) at reflux overnight. The mixture was partitioned between diethyl ether and dilute aqueous HCl. The aqueous phase was made strongly alkaline with sodium hydroxide and reextracted with dichloromethane. The latter extracts were dried over sodium sulphate. After evaporation of the solvents, the residue was purified by column chromatography, eluting sequentially with CH₂Cl₂; 5%MeOH/CH₂Cl₂; 5%MeOH/1%NH₄OH/CH₂Cl₂ giving a light brown gum.

Yield = 150mg (ca quantitative)

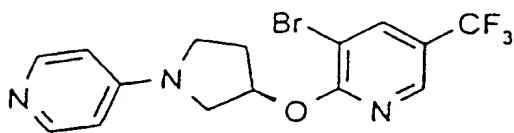
10 $R_f = 0.28$ (5%MeOH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): $\delta = 2.38$ (m, 5H), 3.75 (m, 4H), 5.78 (m, 1H), 6.18 (s, 1H), 6.80 (d, 1H), 7.78 (dd, 1H), 8.42 (s, 1H), 8.50 (s, 1H).

MS (ESP+): m/e 325 (M+H)⁺.

15 Example 128

(3R)-1-(4-pyridyl)-3-(3-bromo-5-trifluoromethyl-2-pyridyloxy)pyrrolidine



20 Scale: 11.5mmol

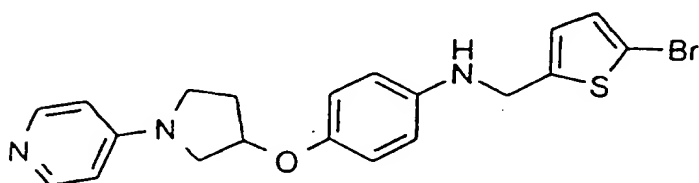
Method E. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 3-bromo-5-trifluoromethyl-(2H)-pyridone. The residue was purified by column chromatography, eluting sequentially with CH₂Cl₂; 5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂ giving an off-white solid.

25 Yield = 580mg (13%)

$R_f = 0.28$ (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): $\delta = 2.40$ (m, 2H), 3.55 (m, 3H), 3.80 (dd, 1H), 5.78 (m, 1H), 6.40 (d, 2H), 8.02 (m, 1H), 8.22 (d, 2H), 8.38 (m, 1H).

MS (ESP-): m/e 388/390 (M+H)⁺.

Example 1291-(4-pyridyl)-3-(4-(5-bromo-2-thiophenylmethylamino)phenoxy)pyrrolidine

5

Scale: 1.57mmol

1-(4-pyridyl)-3-(4-aminophenoxy)pyrrolidine (made from 1-(4-pyridyl)-3-hydroxypyrrolidine by alkylation with 4-fluoronitrobenzene followed by hydrogenation) (400mg, 1eq) and 5-bromo-2-thiophenecarboxaldehyde (330mg, 1.1eq) were dissolved in methanol (8ml) and cooled in ice-water. The mixture was acidified to pH4 with glacial acetic acid. Sodium cyanoborohydride (103mg, 1.05eq) was added portionwise. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours before partitioning between CH_2Cl_2 and 10% aqueous sodium carbonate solution.

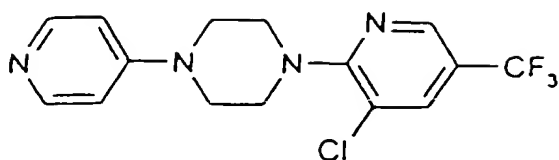
15 The organic layer was washed with water and brine, dried over magnesium sulphate and concentrated. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 2%MeOH/ CH_2Cl_2 ; 4%MeOH/ CH_2Cl_2 ; 5%MeOH/0.5% NH_4OH / CH_2Cl_2 giving a light brown solid.

Yield = 341mg (50%)

20 $R_f = 0.45$ (10%MeOH/1% NH_4OH / CH_2Cl_2)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.22 (m, 1H), 2.38 (m, 1H), 3.5 (m, 4H), 4.40 (s, 2H), 4.98 (m, 1H), 6.41 (m, 2H), 6.62 (m, 2H), 6.78 (m, 3H), 6.90 (s, 1H), 8.21 (d, 2H).

MS (ESP+): m/e 430/432 ($\text{M}+\text{H}$) $^+$.25 **Example 130**1-(4-pyridyl)-4-(3-chloro-5-trifluoromethyl-2-pyridyl)piperazine

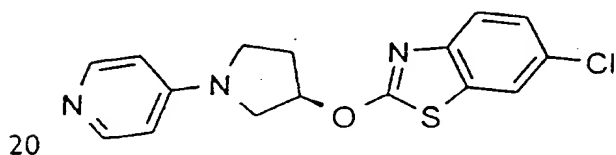


Scale: 3.07mmol

- 5 Method: 1-Pyridyl piperazine (500mg) was heated at reflux in THF (10ml) with 2,3-dichloro-5-trifluoromethylpyridine (662mg, 1 eq) and triethylamine (0.470ml, 1.1eq) for 18 hours. The mixture was partitioned between dichloromethane and water. The organic layer was dried over sodium sulphate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel, eluting sequentially with CH₂Cl₂; 3%MeOH/CH₂Cl₂;
 10 6%MeOH/CH₂Cl₂, giving the product as a yellow solid.
 Yield = 602mg (57%)
 R_f = 0.45 (10%MeOH/1%NH₄OH/CH₂Cl₂)
¹H-NMR (250MHz, CDCl₃): δ = 3.5 (m, 4H), 3.68 (m, 4H), 6.72 (dm, 2H), 7.80 (d, 1H), 8.32 (dm, 2H), 8.42 (m, 1H).
 15 MS (CI): m/e 343 (M+H)⁺.

Examples 131/132

(3R)-1-(4-pyridyl)-3-(6-chlorobenzthiazol-2-yl)oxy)pyrrolidine



Scale: 1.82mmol

- Method A. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,6-dichlorobenzthiazole. The
 25 residue was purified by column chromatography, eluting sequentially with CH₂Cl₂; EtOAc;
 5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving a brown solid
 which was triturated with ether.

Yield = 315mg (36%)

R_f = 0.38 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (200MHz, CDCl₃): δ = 2.40 (m, 1H), 2.54 (m, 1H), 3.58 (m, 2H), 3.78 (m, 2H), 5.87 (m, 1H), 6.44 (d, 2H), 7.36 (dd, 1H), 7.62 (m, 2H), 8.23 (d, 2H).

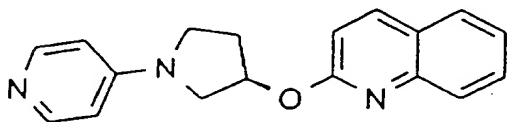
5 MS (ESP+): m/e 332 (M+H)⁺.

The (R) enantiomer was also prepared by the same method, and gave identical analytical data.

Example 133

(3R)-1-(4-pyridyl)-3-(2-quinolyloxy)pyrrolidine

10



Scale: 1.83mmol

15 Method A, using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloroquinoline in 1ml THF.

The residue was purified by column chromatography, eluting sequentially with CH₂Cl₂;

5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving an off-white solid.

Yield = 500mg (94%)

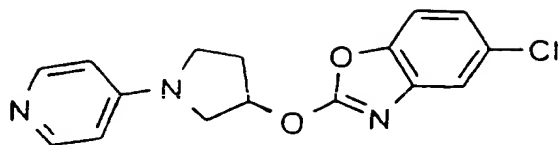
20 R_f = 0.37 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): δ = 2.42 (m, 2H), 3.58 (m, 3H), 3.82 (dd, 1H), 5.96 (m, 1H), 6.42 (d, 2H), 6.84 (d, 1H), 7.40 (t, 1H), 7.63 (t, 1H), 7.72 (d, 1H), 7.98 (d, 1H), 8.20 (d, 2H).

MS (ESP+): m/e 292 (M+H)⁺.

25 Examples 134/135

(3R)-1-(4-pyridyl)-3-(5-chlorobenzoxazol-2-yloxy)pyrrolidine



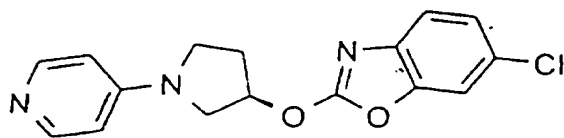
Scale: 175mg, 1.07mmol

- 5 Method A (without tetrabutylammonium bromide) in THF (0.5M), using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,6-dichlorobenzoxazole, with 1hr reaction time. After evaporation of the solvent, the residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving an off-white powder.
- 10 Yield = 79mg (23%)
 $R_f = 0.54$ (10%MeOH/1% NH_4OH / CH_2Cl_2)
 $^1\text{H-NMR}$ (300MHz, CDCl_3): $\delta = 2.42$ (m, 1H), 2.58 (m, 1H), 3.61 (m, 2H), 3.78 (m, 2H), 5.75 (m, 1H), 6.42 (d, 2H), 7.18 (dd, 1H), 7.25 (m, 1H), 7.47 (s, 1H), 8.22 (d, 2H).
 MS (ESP+): m/e 316/318 ($\text{M}+\text{H}$) $^+$.
- 15 The (S) enantiomer was also prepared by the same method in 46% yield from the (S) alcohol, and gave identical analytical data.

Example 136

(3R)-1-(4-pyridyl)-3-(6-chlorobenzoxazol-2-yl)pyrrolidine

20



Scale: 1.27mmol

- 25 Method A, using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2,6-dichlorobenzoxazole in 1ml THF. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ;

5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving an off-white solid.

Yield = 25mg (6%)

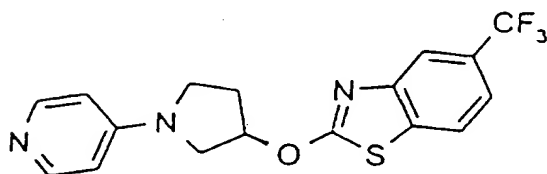
R_f = 0.46 (10%MeOH/1%NH₄OH/CH₂Cl₂)

¹H-NMR (300MHz, CDCl₃): δ = 2.42 (m, 1H), 2.60 (m, 1H), 3.60 (m, 2H), 3.80 (m, 2H), 5.75 (m, 1H), 6.42 (d, 2H), 7.25 (m, 1H + CHCl₃), 7.40 (m, 2H), 8.22 (m, 2H).

MS (ESP+): m/e 316/318 (M+H)⁺.

Example 137

10 (3R)-1-(4-pyridyl)-3-(5-(5-trifluoromethylbenzthiazol-2-yloxy)pyrrolidine



Scale: 2.44mmol

15

Method A, using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-(methanesulphonyl)-5-trifluoromethylbenzthiazole. The residue was purified by column chromatography, eluting sequentially with CH₂Cl₂; EtOAc; 5%MeOH/CH₂Cl₂; 10%MeOH/CH₂Cl₂; 10%MeOH/1%NH₄OH/CH₂Cl₂ giving a pale yellow solid.

20 Yield = 185mg (21%)

R_f = 0.37 (10%MeOH/1%NH₄OH/CH₂Cl₂)

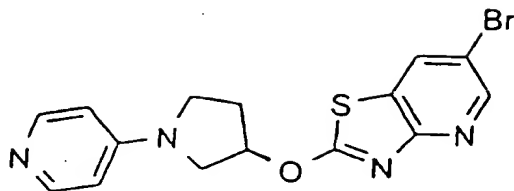
¹H-NMR (300MHz, CDCl₃): δ = 2.41 (m, 1H), 2.58 (m, 1H), 3.58 (m, 2H), 3.78 (m, 2H), 5.88 (m, 1H), 6.42 (d, 2H), 7.48 (d, 1H), 7.77 (d, 1H), 7.88 (s, 1H), 8.22 (d, 2H).

MS (ESP+): m/e 366 (M+H)⁺.

25

Example 138

(3R)-1-(4-pyridyl)-3-(6-bromothiazolo[4,5-b]pyridin-2-yloxy)pyrrolidine



Scale: 355mg, 2.17mmol

5 Method B, using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-methanesulphonyl-4-aza-6-bromobenzthiazole, with 1hr reaction time. After evaporation of the solvent, the residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving a pale yellow solid.

Yield = 128mg (16%)

10 R_f = 0.47 (10%MeOH/1% NH_4OH / CH_2Cl_2)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.42 (m, 1H), 2.60 (m, 1H), 3.60 (m, 2H), 3.80 (m, 2H), 5.98 (m, 1H), 6.42 (d, 2H), 8.11 (s, 1H), 8.22 (d, 2H), 8.58 (s, 1H).

MS (ESP+): m/e 377/379 ($\text{M}+\text{H}$) $^+$.

15 2-Methanesulphonyl-4-aza-6-bromobenzthiazole was made in three steps from 2-amino-3,5-dibromopyridine as follows:

2-Thio-4-aza-6-bromobenzthiazole

2-Amino-3,5-dibromopyridine (5.21g, 20.7mmol) and ethyl potassium xanthate (6.28g, 41.3mmol) were heated together in N-methylpyrrolidine (42ml) at 170°C for three hours. The mixture was dissolved in hot water (ca. 150ml) and filtered whilst hot. Upon cooling, the filtrate was acidified with acetic acid. The resulting precipitate was filtered, washed with water and dried to give the product.

Yield = 4.48g (87%)

25 $^1\text{H-NMR}$ (300MHz, $\text{d}_6\text{-DMSO}$): δ = 8.38 (s, 1H), 8.45 (s, 1H).

MS (CI^+): m/e 247/249 ($\text{M}+\text{H}$) $^+$.

2-Methylthio-4-aza-6-bromobenzthiazole

2-Thio-4-aza-6-bromobenzthiazole (4.45g, 18.02mmol) and potassium carbonate (2.99g, 1.2 equivalents) were mixed in DMF (40ml). Iodomethane (1.13ml, 1.0 equivalents) was added dropwise. After stirring for three hours the mixture was partitioned between diethyl ether and water. The organic layer was dried over sodium sulphate, filtered and evaporated to give a dark oil. This was purified by column chromatography, eluting sequentially with CH_2Cl_2 and then diethyl ether.

Yield = 1.3g (28%)

R_f = 0.66 (50%EtOAc/ CH_2Cl_2)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.79 (s, 3H), 8.15 (s, 1H), 8.55 (s, 1H).

MS (CI+): m/e 261/263 ($\text{M}+\text{H}$) $^+$.

2-Methanesulphonyl-4-aza-6-bromobenzthiazole

2-Methylthio-4-aza-6-bromobenzthiazole (1.02g, 3.9mmol) was dissolved in acetic acid (10ml) and a solution of potassium permanganate (1.36g, 2.2 equivalents) in water (10ml) was added with sufficient cooling in ice as to keep the reaction temperature at 25-30°C. After stirring for an hour at room temperature the black reaction mixture was treated with sodium metabisulphite, giving a white suspension. The pH was adjusted to ca 8-9 with 20% aqueous ammonia. The mixture was extracted with ethyl acetate, and the combined organic phases were dried over sodium sulphate, filtered and evaporated to give an orange-cream solid.

Yield = 0.71g (62%)

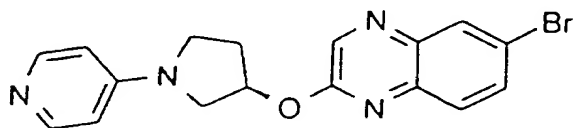
R_f = 0.58 (50%EtOAc/ CH_2Cl_2)

$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 3.42 (s, 3H), 8.55 (s, 1H), 8.85 (s, 1H).

MS (CI+): m/e 293/295 ($\text{M}+\text{H}$) $^+$.

Examples 139/140

(3R)-1-(4-pyridyl)-3-(6-bromo-2-quinoxalinyloxy)pyrrolidine



Scale: 0.63mmol

Method B. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-chloro-6-bromoquinoxaline. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving a yellow solid.

Yield = 200mg (85%)

R_f = 0.34 (10%MeOH/1% NH_4OH / CH_2Cl_2)

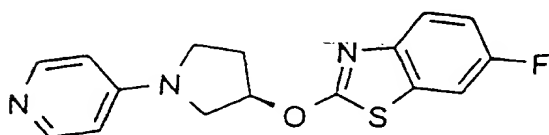
$^1\text{H-NMR}$ (200MHz, CDCl_3): δ = 2.42 (m, 2H), 3.60 (m, 3H), 3.84 (dd, 1H), 5.94 (m, 1H), 6.44 (d, 2H), 7.77 (m, 2H), 8.21 (m, 3H), 8.43 (s, 1H).

10 MS (ESP+): m/e 371/373 ($\text{M}+\text{H}$) $^+$.

The (S) enantiomer was also prepared by the same method in 30% yield from the (S) alcohol, and gave identical analytical data.

Example 141

15 (3R)-1-(4-pyridyl)-3-(6-fluorobenzthiazol-2-yl)oxy)pyrrolidine



Scale: 2.44mmol

20

Method B. using (R)-1-(4-pyridyl)-3-hydroxypyrrolidine and 2-(isopropylsulphonyl)-6-trifluoromethylbenzthiazole. The residue was purified by column chromatography, eluting sequentially with CH_2Cl_2 ; EtOAc; 5%MeOH/ CH_2Cl_2 ; 10%MeOH/ CH_2Cl_2 ; 10%MeOH/1% NH_4OH / CH_2Cl_2 giving an off-white solid.

25 Yield = 498mg (65%)

R_f = 0.42 (10%MeOH/1% NH_4OH / CH_2Cl_2)

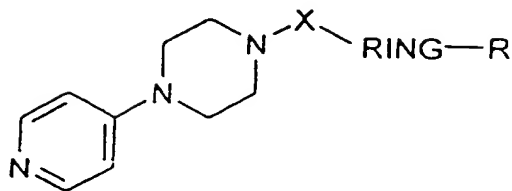
$^1\text{H-NMR}$ (300MHz, CDCl_3): δ = 2.35 (m, 1H), 2.45 (m, 1H), 3.48 (m, 2H), 3.66 (m, 2H), 5.78 (m, 1H), 6.38 (d, 2H), 7.03 (m, 1H), 7.25 (m, 1H), 7.55 (m, 1H), 8.18 (d, 2H).

MS (ESP+): m/e 316 ($\text{M}+\text{H}$) $^+$.

Example 142

The following compounds were also prepared using the methods described below.

5



10

Compound	X	RING	R	mp °C	Method
1	CH ₂	phenyl	4-cyano	95-98	B
2	CH ₂	2-furanyl	H	OIL*	A
3	CH ₂	4-pyrimidinyl	2,6-dichloro	>300	B
4	CH ₂	4-thiazolyl	2-(4)-chlorophenyl	151-152	B
5	CH ₂	4-oxazolyl	2-(4)-bromophenyl	192-193	B
6	CH ₂	phenyl	4-methanesulphone	200-202	B
7	-	phenyl	3-nitro	145-147	C
8	-	phenyl	3-methyl-4-nitro	158-160	C
9	-	phenyl	3-trifluoromethyl-4-nitro	168-170	C

* ¹H NMR (CDCl₃): 2.55(4H,t), 3.34(4H,t), 6.23(1H,d), 6.33(1H,t), 6.64(2H,d), 7.4(1H,d), 8.25(2H,d)

15

Method A :

490 mg 4-pyridylpiperazine, 498 mg sodium acetate, and 0.38 ml 2-furaldehyde was stirred in 12 ml methanol containing 3 g 3A^o molecular sieve powder. 377 mg sodium

cyanoborohydride was added and stirring continued overnight. The sieve was filtered and the filtrate concentrated and stirred with 25 ml 2 M sodium hydroxide solution. Extraction with dichloromethane and drying over MgSO_4 , followed by evaporation and chromatography (10 g Bond Elute, CH_2Cl_2 , then 1% methanol/ CH_2Cl_2 /1% NH_4OH) gave compound 2 (214 mg) as a colourless oil.

Method B :

490 mg 4-pyridylpiperazine and 614 mg 4-chloromethylphenyl methyl sulphone in 1.8 ml isopropanol and 0.2 ml water with 1.4 ml triethylamine was refluxed for 1.25 hours, then stirred overnight at ambient temperature. The solvent was evaporated, the residue dissolved in dichloromethane and washed with 5% w/v sodium hydroxide solution followed by water and brine, then dried over MgSO_4 . Evaporated then chromatographed (as in Method A above) to give compound 6 (640mg). Compounds 1, 3, 4 and 5 were prepared in an analogous manner.

15

Method C :

980 mg pyridylpiperazine and 1.0 g 2-methyl-4-fluoronitrobenzene with 1.8 g anhydrous potassium carbonate in 10 ml DMSO was heated at 125° C overnight. The mixture was diluted with dichloromethane and washed with water and brine. Dried, evaporated and chromatographed as above in Method A to give compound 8 (903mg). Compounds 7 and 9 were prepared in a similar manner.

Example 143

25 Illustrative pharmaceutical dosage forms suitable for presenting the compounds of the invention for therapeutic or prophylactic use include the following tablet and capsule formulations, which may be obtained by conventional procedures well known in the art of pharmacy and are suitable for therapeutic or prophylactic use in humans:-

(a) Tablet I		mg/tablet
Compound Z*		1.0
Lactose Ph. Eur.		93.25
5 Croscarmellose sodium		4.0
Maize starch paste (5% w/v aqueous paste)		0.75
Magnesium stearate		1.0
(b) Tablet II		mg/tablet
10 Compound Z*		50
Lactose Ph. Eur.		223.75
Croscarmellose sodium		6.0
Maize starch		15.0
Polyvinylpyrrolidone (5% w/v aqueous paste)		2.25
15 Magnesium stearate		3.00
(c) Tablet III		mg/tablet
Compound Z*		100
Lactose Ph. Eur.		182.75
20 Croscarmellose sodium		12.0
Maize starch paste (5% w/v aqueous paste)		2.25
Magnesium stearate		3.0
(d) Capsule		mg/capsule
25 Compound Z*		10
Lactose Ph. Eur.		488.5
Magnesium stearate		1.5

Note

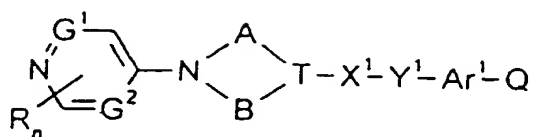
* The active ingredient Compound Z is a compound of formula I, or a salt thereof, for
 30 example a compound of formula I described in any of the preceding Examples.

The tablet compositions (a) - (c) may be enteric coated by conventional means, for example, with cellulose acetate phthalate.

CLAIMS

1. A compound of formula I, or a pharmaceutically acceptable salt thereof.

5



wherein

G^1 is CH or N;

G^2 is CH or N;

10 n is 1 or 2;

R is hydrogen, halogeno, trifluoromethyl, trifluoromethoxy, cyano, amino, hydroxy, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino, di(1-4C)alkylamino or phenyl(1-4C)alkyl;

A is methylene or ethylene; B is ethylene; and wherein A and B may independently
15 optionally bear a substituent selected from (1-6C)alkyl, (1-6C)alkoxy, phenyl(1-4C)alkyl, halogeno and (1-6C)alkoxycarbonyl;

T is CH, or N;

when T is CH, X^1 is selected from CR^1R^2 , SO_2 , SO , CO , CR^3R^4O , a bond, O, S and NR^5 ; and when T is N, X^1 is selected from CR^1R^2 , SO_2 , SO , CO , CR^3R^4O and a bond;

20 wherein R^1 , R^2 , R^3 , R^4 and R^5 are independently selected from hydrogen and (1-4C)alkyl;

Y^1 represents CR^6R^7 or a bond, wherein R^6 and R^7 are independently selected from hydrogen and (1-4C)alkyl;

Ar^1 is a phenylene, naphthylene, a 5- or 6-membered monocyclic heteroaryl ring containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur, or a 9- or 10-
25 membered bicyclic heteroaryl ring containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur;

Q is selected from hydrogen and a group of formula $L^1X^2L^2Z$ in which L^1 is a bond, (1-4C)alkylene or (2-4C)alkenylene, L^2 is a bond or (1-4C)alkylene, X^2 is a bond, O, S, SO , SO_2 , CR^8R^9 , CO , OSO_2 , OCR^8R^9 , OCO , SO_2O , $CR^8(R^9)O$, COO , $NR^{10}SO_2$, SO_2NR^{10} ,
30 $NR^{11}CO$, $CONR^{11}$, $NR^{12}CONR^{13}$ and NR^{14} in which R^8 and R^9 are independently selected from hydrogen, hydroxy and (1-4C)alkyl; and

R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are independently selected from hydrogen and (1-4C)alkyl;

Z is hydrogen, (1-4C)alkyl, phenyl, naphthyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl or a heterocyclic moiety containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur;

5 and wherein the phenyl, naphthyl or heteroaryl moiety in Ar^1 and the alkyl, phenyl, naphthyl, or heterocyclic moiety in Z may optionally bear one or more substituents selected from halogeno, hydroxy, oxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, hydroxy(1-6C)alkyl, (1-6C)alkoxy, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (1-4C)alkylenedioxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-10 (1-6C)alkylcarbamoyl, di-N[(1-6C)alkyl]carbamoyl, (1-6C)alkanoylamino, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, (1-6C)alkanoyl, tetrazoyl, phenyl, phenoxy, phenylsulphonylpiperidinocarbonyl, morpholinocarbonyl, hydroxy(1-6C)alkyl and amino(1-6C)alkyl; wherein any phenyl containing substituents may optionally bear one or more
15 substituents selected from halogeno, trifluoromethyl, trifluoromethoxy, cyano, amino, hydroxy, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino and di(1-4C)alkylamino; provided that the compound is not N-[4-[4-(4-pyridyl)piperazin-1-ylcarbonyl]phenyl]-(E)-4-chlorostyrenesulphonamide or N-[4-[4-(4-pyridyl)piperazin-1-ylcarbonyl]phenyl]-4'-bromo-4-biphenylesulphonamide;

20 and pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1 wherein there is provided a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein

G^1 is CH or N;

25 G^2 is CH or N;

n is 1 or 2;

R is hydrogen, halogeno, trifluoromethyl, trifluoromethoxy, cyano, amino, hydroxy, nitro, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylamino or di(1-4C)alkylamino;

A is methylene or ethylene; B is ethylene; and wherein A and B may independently
30 optionally bear a substituent selected from (1-6C)alkyl, (1-6C)alkoxy, phenyl (1-4C)alkyl, halogeno and (1-6C)alkoxycarbonyl;

T is CH or N;

when T is CH, X^1 is selected from CR^1R^2 , SO_2 , SO , CO , a bond, CR^3R^4O , O , S and NR^5 , and when T is N, X^1 is selected from CR^1R^2 , SO_2 , SO , CO , CR^3R^4O and a bond, wherein R^1 , R^2 , R^3 , R^4 and R^5 are independently selected from hydrogen and (1-4C)alkyl;

Y^1 represents CR^6R^7 or a bond, wherein R^6 and R^7 are independently selected from
5 hydrogen and (1-4C)alkyl;

Ar^1 is a phenylene ring or a 5- or 6-membered monocyclic heteroaryl ring containing 1, 2 or 3 heteroatoms selected from nitrogen, oxygen and sulphur;

Q is selected from hydrogen and a group of formula $L^1X^2L^2Z$ in which L^1 is a bond or (1-4C)alkylene, L^2 is a bond or (1-4C)alkylene, X^2 is a bond, S , SO , SO_2 , CR^8R^9 , CO ,
10 $NR^{10}SO_2$, SO_2NR^{11} , $NR^{12}CO$, $CONR^{12}$ and $NR^{13}CONR^{14}$ in which R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} and R^{14} are independently selected from hydrogen and (1-4C)alkyl;

Z is selected from phenyl, naphthyl, phenyl(2-4C)alkenyl, phenyl(2-4C)alkynyl and a heterocyclic moiety containing 1, 2, 3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur;

15 and wherein the phenyl or heteroaryl moiety in Ar^1 and the phenyl, naphthyl, or heterocyclic moiety in Z may optionally bear one or more substituents selected from halogeno, hydroxy, amino, nitro, cyano, carboxy, carbamoyl, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (3-6C)cycloalkyl, (3-6C)cycloalkyl(1-4C)alkyl, (1-4C)alkylenedioxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, N-(1-6C)alkylcarbamoyl, di-
20 N[(1-6C)alkyl]carbamoyl, (1-6C)alkanoylamino, (1-6C)alkoxycarbonyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, halogeno(1-6C)alkyl, halogeno(1-6C)alkoxy, (1-6C)alkanoyl and tetrazoyl;

provided that the compound is not N-[4-{4-(4-pyridyl)piperazin-1-ylcarbonyl}phenyl]-(E)-4-chlorostyrenesulphonamide,

25 and pharmaceutically acceptable salts thereof.

3. A compound as claimed in claim 1 or 2 wherein Q is H, T is CH or N; when T is CH, X^1 is O , S , CO , SO_2 , CH_2 or a bond; when T is N, X^1 is CO , SO_2 or CH_2 ; Y^1 is a bond and G is CH.

30

4. A compound as claimed in claim 1 or 2 wherein Q is H, R and n are as defined in claim 1 or 2 and G^1 , G^2 , T, X^1 , R^1 , R^2 , R^3 , Y^1 , A, B and Ar^1 are selected from:

(a) G^2 is CH or N; G^1 is CH; T is N or CH; when T is N, X^1 is CR^1R^2 , SO_2 , CO; when T is CH, X^1 is CR^1R^2 , SO_2 , CO, O, S, NR^3 or a bond, in which R^1 , R^2 and R^3 are independently

5 selected from hydrogen and (1-4C)alkyl; Y^1 is a bond. A and B are both ethylene; Ar^1 is a phenyl ring;

(b) G^2 is CH or N; G^1 is CH, T is N, X^1 is CH_2 , SO_2 or CO, A and B are ethylene, Y^1 is a bond. Ar^1 is a phenyl ring;

(c) G^2 is CH, G^1 is CH, T is N, X^1 is CH_2 , SO_2 or CO. A and B are ethylene, Y^1 is a bond, 10 Ar^1 is a phenyl ring;

(d) G^2 is CH or N, G^1 is CH, T is CH, A is methylene, B is ethylene, X^1 is O or a bond, Y^1 is a bond. Ar^1 is a phenyl or pyridyl ring; or

(e) G^2 is CH or N, G^1 is CH, T is N, X^1 is CH_2 , SO_2 , CO, A and B are ethylene, Y^1 is a bond, Ar^1 is a pyridyl ring.

15

5. A compound as claimed in claim 1 or 2 wherein G^1 is CH, G^2 is CH, T is N, X^1 is CO, SO_2 or CH_2 , A and B are ethylene, Ar^1 is phenyl and, Q is hydrogen.

6. A compound as claimed in claim 1 or 2 wherein Q is a group of formula $L^1X^2L^2Z$ and 20 X^1 is a bond.

7. A compound as claimed in claim 1 or 2 wherein R and n are as defined in claim 1 or 2 and G^1 , G^2 , T, A, B, X^1 , Y^1 , and Q are selected from:

(a) G^2 is CH or N, G^1 is CH, T is N or CH, A is ethylene, or methylene, B is 25 ethylene. X^1 and Y^1 are bonds, Q is a group of formula $L^1X^2L^2Ar^2$ in which L^1 is (1-4C)alkylene or a bond, X^2 is selected from $CONR^{12}$, $NR^{12}CO$, $NR^{10}SO_2$, $NR^{13}CONR^{14}$ and SO_2 , L is a (1-4C)alkylene or a bond, R^{10} , R^{12} , R^{13} and R^{14} are independently selected from hydrogen and (1-4C)alkyl;

(b) G^2 is CH or N, G^1 is CH, T is N or CH, A and B are ethylene. X^1 and Y^1 are bonds; Q 30 is a group of formula $L^1X^2L^2Ar^2$ in which L^1 is (1-4C)alkylene or a bond, X^2 is $NHCO$, $NHSO_2$, $NHCONH$ or SO_2 , L^2 is (1-4C)alkylene or a bond, and R and n are as hereinbefore defined;

- (c) G^1 is CH. G^1 is CH. T is N or CH. A and B are ethylene, X^1 and Y^1 are bonds. Q is $L^1X^2L^2Ar^2$ in which L^1 is (1-4C)alkylene. L^2 is a bond, X^2 is NHCO, $NHSO_2$, $NHCONH$ and SO_2 , or
- (d) G^2 is CH or N (preferably CH), G^1 is CH; T is N or CH (preferably N), X^1 and Y^1 are bonds. A and B are ethylene. Ar^1 is phenyl, Q is a group of formula $L^1X^2L^2Ar^2$ in which L^1 is (1-4C)alkylene or a bond (preferably alkylene such as CH_2), X^2 is NHCO, $NHSO_2$, $NHCONH$ or SO_2 , L^2 is (1-4C)alkylene or a bond (preferably a bond).
8. A compound as claimed in any one of claims 1 to 7 wherein G^1 and G^2 are each CH.
9. A compound as claimed in claim 1 or 2 wherein G^1 is CH, G^2 is CH, T is N, X^1 is a bond. Y^1 is a bond. A and B are ethylene, Ar^1 is phenyl, Q is of formula $L^1X^2L^2Z$ in which L^1 is (1-4C)alkylene (preferably CH_2), X^2 is NR^6SO_2 in which R^6 is (1-4C)alkyl or hydrogen (preferably hydrogen), and Z is phenyl, wherein the phenyl moiety of Ar^1 and Z may optionally be substituted as defined in claim 1 or 2 and R and n are as defined in claim 1 or 2.
10. A compound of the formula I as claimed in claim 1 wherein
 G^1 is CH,
 G^2 is CH or N
- 20 T is CH or N, when T is CH then X^1Y^1 together are O or S, when T is N then X^1Y^1 together are a bond.
- Ar^1 is a phenylene ring, a pyridyl ring, or a fused heterocyclic system containing 1,2 or 3 heteroatoms, and may optionally bear one or more substituents selected from halogeno, nitro, cyano, (1-6C) alkyl, (1-6C)alkylthio, halogeno(1-6C)alkyl, halogeno(1-6C)alkylthio, halogeno(1-6C)alkoxy, (1-6C)alkoxycarbonyl,
- Q is selected from hydrogen and a group of formula $L^1X^2L^2Ar^2$ in which L^1 is a bond or (1-4C)alkylene, L^2 is a bond or (1-4C)alkylene, X^2 is a bond, NR^8 , O or S, in which R^8 is hydrogen or (1-4)C alkyl; and
- Ar^2 is selected from phenyl, and a monocyclic heterocyclic moiety containing 1,2,3 or 4 heteroatoms selected from nitrogen, oxygen and sulphur, and may optionally bear one or more substituents selected from halogeno, nitro, cyano, (1-6C) alkyl, (1-6C)alkylthio, halogeno(1-6C)alkyl, halogeno(1-6C)alkylthio, halogeno(1-6C)alkoxy, (1-6C)alkoxycarbonyl;

11. A compound as claimed in any one of claims 1-10 wherein Ar^1 is a phenylene ring, a 2-pyridyl ring, a benzthiazol-2-yl ring, a 2-quinoyloxy ring, a benzoxazolyl ring, a thiazolopyridin-2-yl or a quinoxalinyloxy ring.

12. A compound as claimed in any one of claims 1-11 wherein R is hydrogen, halogeno or (1-4C)alkyl.

13. A compound as claimed in any one of claims 1-12 wherein the substituent Q on Ar^1 is in the 4-position.

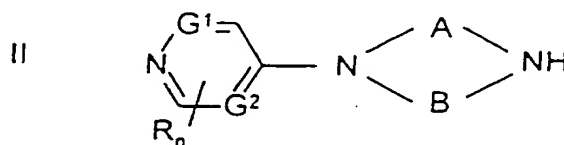
10

14. A compound as claimed in any one of claims 1-13 wherein the substituent(s) on Ar^1 and/or Ar^2 are independently selected from methyl, methylthio, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, chlorine, bromine, fluorine and methoxycarbonyl.

15. A process for preparing a compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 which process is selected from:

(a) for the production of those compounds of the formula I wherein T is N and X' is CO, the reaction, conveniently in the presence of a suitable base, of an amine of the formula II,

20



with an acid of the formula III.

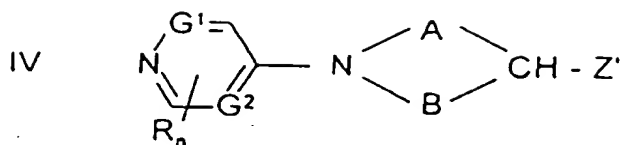
25



or a reactive derivative thereof.

(b) for the production of those compounds of the formula I wherein T is CH and X' is O the reaction of a compound of the formula IV

30



5

wherein Z' is a displaceable group, with a compound of the formula V;



10

(c) for the production of those compounds of the formula I wherein T¹ is N and X¹ is CH(R²), the reductive amination of a keto compound of the formula VI,



15

with an amine of the formula II.

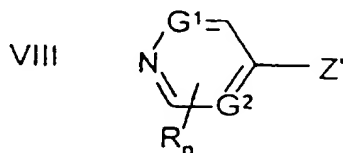
(d) The reaction of an amine of formula II with a compound of formula VII;



20

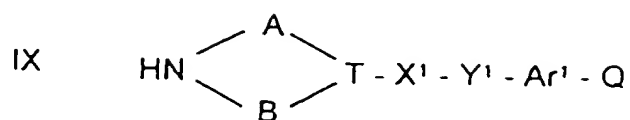
wherein Z' is a displaceable group;

(e) the reaction of a compound of formula VIII



25

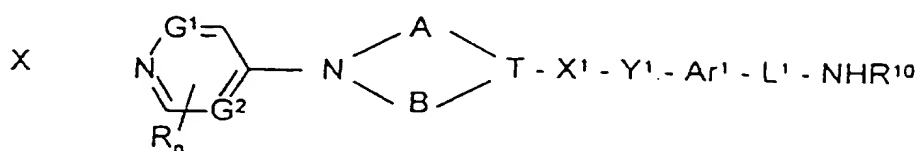
wherein Z' is a displaceable group with a compound of formula IX



5

(f) for the production of those compounds of the formula I wherein X² is a group of the formula NR¹⁰SO₂, the reaction of an amine of the formula X

10



with a compound of the formula XI,

15

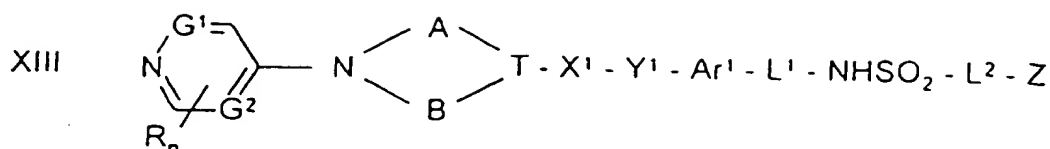


wherein Z' is a displaceable group;

(g) for the production of those compounds of the formula I wherein X² is a group of the formula NR¹³CONR¹⁴, the reaction of an amine of the formula X, with a compound of the formula XII;



25 (h) for the production of those compounds of the formula I wherein X² is a group of the formula NR¹⁰SO₂ and R¹⁰ represents (1-4C)alkyl, the reaction of a corresponding sulphonamide of the formula XIII.



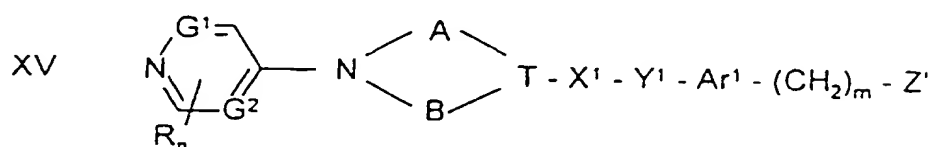
5 with a compound of the formula XIV,



XIV

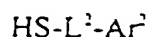
wherein Z' is a displaceable group;

- 10 (i) for the production of those compounds of the formula I wherein L' represents (1-4C)alkylene and X^2 is S, the reaction of a compound of the formula XV,



15

wherein m is 1,2,3 or 4, and Z' is a displaceable group with a thiol of the formula XVI;



XVI

- (j) for the production of those compounds of the formula I wherein Ar^1 or Z bears a
 20 carboxy or carboxy-containing group, the hydrolysis of a compound of the formula I wherein Ar^1 or Z bears a (1-6C)alkoxycarbonyl group.
 (k) for the production of those compounds of the formula I wherein Ar^1 or Z bears a carbamoyl, N -(1-6C)alkylcarbamoyl or alkyl-di- N [(1-6C)carbamoyl] group, the reaction of a compound of the formula I wherein A^1 or Z bears a carboxy group, or a reactive derivative
 25 thereof, with ammonia or an appropriate alkylamine or dialkylamine.
 (l) for the production of those compounds of the formula I wherein X^1 is a group of the formula SO or SO_2 , wherein Ar^1 or Z bears a (1-6C)alkylsulphinyl or (1-6C)alkylsulphonyl.

substituent or wherein X^2 is a group of the formula SO or SO_2 , the oxidation of the .
corresponding compound of the formula I which contains a thio group;

and whereafter when a pharmaceutically acceptable salt is required reacting the compound of
5 formula I with an acid which affords a physiologically acceptable anion or a base which
affords a physiologically acceptable cation.

16. A pharmaceutical composition comprising a compound of formula I, or a
pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 14, together with
10 a pharmaceutically acceptable carrier or diluent.

17. The use of a compound of formula I, or a pharmaceutically acceptable salt thereof, as
claimed in any one of claims 1 to 14 for the manufacture of a medicament for treating diseases
or medical conditions in which an inhibition of cholesterol biosynthesis is desirable.
15

18. The use of a compound of formula I, or a pharmaceutical acceptable salt thereof, as
claimed in any one of claims 1 to 9 for the manufacture of a medicament for the treatment of
hypercholesterolemia or atherosclerosis.

20 19. Use of a compound as claimed in any one of claims 1-14 as an antifungal agent.

20. A pharmaceutical composition comprising one or more compounds as claimed in any
one of claims 1-14 for use in the treatment of fungal infections of the human or animal body.

INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No.

PCT/GB 97/00282

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/74 C07D239/42 C07D401/12 A61K31/44 C07D401/04
 C07D401/14 C07D405/12 C07D409/12 C07D413/12 C07D417/12
 C07D513/04

According to International Patent Classification (IPC) or to both national classification and IPC

H. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 97 06802 A (ZENECA LTD ;BROWN GEORGE ROBERT (GB); STOKES ELAINE SOPHIE ELISABE) 27 February 1997 see the whole document ---	1-11
X,P	WO 96 10022 A (ZENECA LTD ;FAULL ALAN WELLINGTON (GB); MAYO COLETTE MARIE (GB); P) 4 April 1996 see claims; example 90 ---	1-11
A	FR 2 697 252 A (FOURNIER IND & SANTE) 29 April 1994 see the whole document ---	1-11
X	EP 0 352 946 A (PFIZER LTD ;PFIZER (US)) 31 January 1990 see the whole document ---	1,19
-/-		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

16 May 1997

Date of mailing of the international search report

30.05.97

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Bosma, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 97/00282

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 39 05 364 A (HOECHST AG) 23 August 1990 see the whole document ---	1,16
X	EP 0 244 115 A (PFIZER LTD) 4 November 1987 see the whole document ---	1,16
X	EP 0 233 051 A (PFIZER LTD) 19 August 1987 see the whole document ---	1,16
X	WO 94 22835 A (ZENECA LTD) 13 October 1994 see the whole document -----	1,16

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 97/00282

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3, 6-10, 12-20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see annex

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 97/00282

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The subject matter of the present claims is so broad that a complete search is not possible on economic grounds (PCT Search Guidelines III, 3.6 and 3.7). Therefore the search has been based on the examples of the claims as indicated. The present search report provides only a few examples of novelty destroying documents for the present subject matter.

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